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Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Chlorinated Benzenes. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

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Aquatic Life Toxicology

William A. Brungs, ERL-Narragansett
U.S. Environmental Protection Agency

David J. Hansen, ERL-Gulf Breeze
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects

Albert Munson (author)
Medical College of Virginia

Roy E. Albert*
Carcinogen Assessment Group
U.S. Environmental Protection Agency

Terence M. Grady (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

Donald Barnes
East Carolina University

Jerry F. Stara (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

S.G. Bradley
Medical College of Virginia

John Buccini
Health and Welfare, Canada

Richard A. Carchman
Medical College of Virginia

Herbert Cornish
University of Michigan

Patrick Dugan
Ohio State University

Larry Fishbein
National Center for Toxicological Research

George Fuller
University of Rhode Island

Ronald W. Hart
Ohio State University

Krystyna Locke
U.S. Environmental Protection Agency

Steven D. Lutkenhoff (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

Gordon Newell
National Academy of Sciences

Martha Radike
University of Cincinnati

Larry Rosenstein
SRI International

Sorrell L. Schwartz
Georgetown University

Robert E. McGaughy, CAG
U.S. Environmental Protection Agency

Bonnie Smith, ECAO-Cin
U.S. Environmental Protection Agency

David L. West
National Institute for Occupational Safety and Health

*CAG Participating Members:
Elizabeth L. Anderson, Larry Anderson, Dolph Arnicar, Steven Bayard, David L. Bayliss, Chao W. Chen, John R. Fowle III, Bernard Haberman, Charalingayya Hiremath, Chang S. Lao, Robert McGaughy, Jeffrey Rosenblatt, Dharm V. Singh, and Todd W. Thorslund.

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, T. Highland, R. Rubinstein.

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CRITERIA DOCUMENT

CHLORINATED BENZENES

CRITERIA

Aquatic Life

The available data for chlorinated benzenes indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 250 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of the more toxic of the chlorinated benzenes to sensitive freshwater aquatic life but toxicity occurs at concentrations as low as 50 µg/l for a fish species exposed for 7.5 days.

The available data for chlorinated benzenes indicate that acute and chronic toxicity to saltwater aquatic life occur at concentrations as low as 160 and 129 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Human Health

Monochlorobenzene

For comparison purposes, two approaches were used to derive criterion levels for monochlorobenzene. Based on available toxicity data, for the protection of public health, the derived level is 488 µg/l. Using available organoleptic data, for controlling undesirable taste and odor quality of ambient water, the estimated level is 20 µg/l. It should be recognized that organoleptic data as a basis for establishing a water quality criteria have limitations and have no demonstrated relationship to potential adverse human health effects.

Trichlorobenzenes

Due to the insufficiency in the available information for the trichlorobenzenes, a criterion cannot be derived at this time using the present guidelines.

1,2,4,5-Tetrachlorobenzene

For the protection of human health from the toxic properties of 1,2,4,5-tetrachlorobenzene ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 38 μg/l.

For the protection of human health from the toxic properties of 1,2,4,5-tetrachlorobenzene ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 48 μg/l.

Pentachlorobenzene

For the protection of human health from the toxic properties of pentachlorobenzene ingested through water and contaminated aquatic organisms, the ambient water criterion is determined to be 74 μg/l.

For the protection of human health from the toxic properties of pentachlorobenzene ingested through contaminated aquatic organisms alone, the ambient water criterion is determined to be 85 μg/l.

Hexachlorobenzene

For the maximum protection of human health from the potential carcinogenic effects due to exposure of hexachlorobenzene through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 7.2 ng/l, 0.72 ng/l, and 0.072 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, exlcuding consumption of water, the levels are 7.4 ng/l, 0.74 ng/l, and 0.074 ng/l, respectively.

INTRODUCTION

The chlorinated benzenes, excluding dichlorobenzenes, are monochlorobenzene (C_6H_5Cl), 1,2,3-trichlorobenzene ($C_6H_3Cl_3$), 1,2,4-trichlorobenzene ($C_6H_3Cl_3$), 1,3,5-trichlorobenzene ($C_6H_3Cl_3$), 1,2,3,4-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,3,5-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,4,5-tetrachlorobenzene ($C_6H_2Cl_4$), pentachlorobenzene (C_6HCl_5), and hexachlorobenzene (C_6Cl_6). Based on annual production in the U.S., 139,105 kkg of monochlorobenzene were produced in 1975; 12,849 kkg of 1,2,4-trichlorobenzene, 8,182 kkg of 1,2,4,5-tetrachlorobenzene and 318 kkg of hexachlorobenzene were produced in 1973 (West and Ware, 1977; U.S. EPA, 1975a).

The remaining chlorinated benzenes are produced mainly as by-products from the production processes for the above four chemicals. Production and use of chlorinated benzenes results in 34,278 kkg of monochlorobenzene, 8,182 kkg of trichlorobenzenes and about 1,500 kkg of tetra-, penta-, and hexa-chlorinated benzenes entering the aquatic environment yearly. Annually, 690 kkg of monochlorobenzene and 1,628 kkg of hexachlorobenzene contaminate solid wastes. Yearly estimates of atmospheric contamination of monochlorobenzene and tetrachlorobenzenes are 362 and 909 kkg, respectively (West and Ware, 1977).

Chlorination of benzene yields 12 different compounds: monochlorobenzene (C_6H_5Cl), three isomers of dichlorobenzene (the subject of another criterion document), three trichlorobenzenes, three tetrachlorobenzenes, pentachlorobenzene and hexachlorobenzene.

All are colorless liquids or solids with a pleasant aroma. The most important properties imparted by chlorine to these compounds are solvent power, viscosity, and moderate chemical reactivity. All of the chlorobenzenes are heat stable (Kirk and Othmer, 1963; Snell, et al. 1969; Hampel and Hawley, 1973; Stecher, 1968; Mardsen and Marr, 1963).

Viscosity data are not available for all the chlorinated benzenes. Nevertheless, the trend is for viscosity to increase from chlorobenzene to the more highly chlorinated benzenes. The nonflammability of these compounds follows the same trend. Chlorobenzene is flammable; trichlorobenzene is nonflammable but gives off combustable fumes; the remaining compounds are nonflammable (Kirk and Othmer, 1963; Mardsen and Marr, 1963).

Vapor pressures of the chlorinated benzenes decrease progressively from monochlorobenzene to hexachlorobenzene, i.e., at 60°C, the vapor pressures of monochlorobenzene, trichlorobenzenes and 1,2,3,5-tetrachlorobenzene are 60, 3 to 4.4 and 2 mm of mercury, respectively (Hampel and Hawley, 1973).

Some physical properties of the chlorinated benzenes are given in Table 1 (Weast, 1975).

Monochlorobenzene, which is the most polar compound, is soluble in water to the extent of 488 mg/l at 25°C (Mellan, 1970; Mardsen and Marr, 1963). Solubilities of the other chlorobenzenes in water were not available. The chlorinated benzenes are generally good solvents for fats, waxes, oils and greases. These compounds have a high lipid solubility and are expected to accumulate in ecosystems (Mardsen and Marr, 1963; Mellan, 1970).

Monochlorobenzene is used for the synthesis of ortho and para nitrochlorobenzenes (50 percent), as a solvent (20 percent), in phenol manufacturing (10 percent) and in DDT manufacturing (7.5 percent). 1,2,4-Trichlorobenzene is used as a dye carrier (46 percent), a herbicide intermediate (28 percent), a heat transfer medium, a dielectric fluid in transformers, a degreaser, a lubricant and a potential insecticide against termites. The

TABLE 1

Physical Properties of Chlorinated Benzenes*

Compound	MW	mp(°C)	bp(°C)	Density	Log Octanol Water Partition
Monochlorobenzene	112.56	-45.6	131-132	1.107	2.83
Trichlorobenzene					
1,2,3-	181.45	52.6	218-219	143	--
1,2,4-	--	17	213.5	1.454	4.23
1,3,5-	--	63.4	208	145	--
Tetrachlorobenzene					
1,2,3,4-	215.90	47.5	254	146	--
1,2,3,5-	--	54.5	246	--	--
1,2,4,5-	--	138-140	243-246	1.858	4.93
Pentachlorobenzene	250.34	86	277	1.858	5.63
Hexachlorobenzene	284.79	230	322	2.044	6.43

*Source: Weast, 1975

other trichlorobenzene isomers are not used in any quantity. 1,2,4,5-Tetrachlorobenzene is the only tetrachloro-isomer used in industrial quantities. Fifty-six percent of the annual consumption of 1,2,4,5-tetrachlorobenzene is used in the production of the defoliant, 2,4,5-trichlorophenoxy acetic acid, 33 percent in the synthesis of 2,4,5-trichlorophenol and 11 percent as a fungicide. Pentachlorobenzene is used in small quantities as a captive intermediate in the synthesis of specialty chemicals (West and Ware, 1977). Hexachlorobenzene in 1972 was used as a fungicide (23 percent) to control wheat bunt and smut on seed grains. Other industrial uses (77 percent) included dye manufacturing, an intermediate in organic synthesis, porosity controller in the manufacturing of electrodes, a wood preservative and an additive in pyrotechnic compositions for the military (U.S. EPA, 1975a).

In recent years, hexachlorobenzene has become of concern because of its widespread distribution as an environmental contaminant and a contaminant of food products used for human consumption. Hexachlorobenzene has been found in adipose tissue and milk of cattle being raised in the vicinity of an industrialized region bordering the Mississippi River between Baton Rouge and New Orleans, Louisiana. Hexachlorobenzene residues have been found in adipose tissue of sheep in western Texas and eastern California (U.S. EPA, 1975b). The occurrence and effects of hexachlorobenzene have been reported in many organisms, e.g., birds (Vos, et al. 1971; Cromartie, et al. 1975), rats (Medline, et al. 1973), man (Cam and Nigogosyan, 1963) and fish (Holden, 1970; Johnson, et al. 1974; Zitko, 1971). Magnification in the natural food chain is indicated by Gilbertson and Reynolds (1972) observation of hexachlorobenzene in the eggs of common terns, which had apparently eaten contaminated fish. This compound has also been found in samples of ocean water, and its persistence in the environment has been acknowledged (Seltzer, 1975).

Specimens of levee soil taken from along the Mississippi River, known to be contaminated with hexachlorobenzene waste, had levels of the compound ranging from 107.0 to 874.0 µg/kg (wet weight) (U.S. EPA, 1976).

Among seven samples of sediments taken from the lower Mississippi River, only one had detectable amounts of hexachlorobenzene. The concentration found was 231 µg/l. This site was known to be contaminated by hexachlorobenzene in the past (Laska, et al. 1976).

The National Organics Reconnaissance Survey (NORS) tested ten water supplies for a variety of organic chemcials. Monochlorobenzene was detected but not quantified in three of the ten drinking water supplies. Drinking water supplies from 83 locations in EPA Region V were analyzed for various pesticides and organic chemicals. Hexachlorobenzene was detected in three locations with concentrations ranging from 6 to 10 ng/l.

The National Organics Reconnaissance Survey tested ten finished drinking waters for a variety of organic chemicals.

REFERENCES

Cam, C. and G. Nigogosyan. 1963. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. Jour. Am. Med. Assoc. 183: 88.

Cromartie, E.W. et al. 1975. Residues of organochlorine pesticides and polychlorinated biphenyls and autopsy data for bald eagles, 1971-1972. Pestic. Monit. Jour. 9: 11.

Gilbertson, M. and L.M. Reynolds. 1972. Hexachlorobenzene (HCB) in the eggs of common terns in Hamilton Harbour, Ontario. Bull. Environ. Contam. Toxicol. 7: 371.

Hampel, C. and G. Hawley. 1973. The Encyclopedia of Chemistry, 3rd ed. Van Nostrand Reinhold Co., New York.

Holden, A.V. 1970. International co-operative study of organochlorine pesticide residues in terrestrial and aquatic wildlife, 1967, 1968, 1970. Pestic. Monit. Jour. 4: 117.

Johnson, J.L., et al. 1974. Hexachlorobenzene (HCB) residues in fish. Bull. Environ. Contam. Toxicol. 11: 393.

Kirk, R.E. and D.F. Othmer. 1963. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed. John Wiley and Sons, New York.

Laska, A.L., et al. 1976. Distribution of hexachlorobenzene and hexachlorobutadiene in water soil and selected aquatic organisms along the lower Mississippi River, Louisiana. Bull. Environ. Contam. Toxicol. 15: 535.

Mardsen, C. and S. Marr. 1963. Solvents Guide. Cleaver-Hume Press Ltd., London.

Medline, A., et al. 1973. Hexachlorobenzene and rat liver. Arch. Pathol. 96: 61.

Mellan, I. 1970. Industrial Solvents. Noyes Data Corp. Park Ridge, New Jersey.

Seltzer, R.J. 1975. Ocean pollutants pose potential danger to man. Chem. Engr. News. 53: 19.

Snell, D., et al. 1969. Encyclopedia of Industrial Chemical Analysis. Vol. 9. Interscience Publishers, New York.

Stecher, P.G. (ed.) 1968. The Merck Index. 9th ed. Merck and Co., Inc., Rahway, New Jersey.

U.S. EPA. 1975a. Survey of industrial processing data: Task I, Hexachlorobenzene and hexachlorobutadiene pollution from chlorocarbon processes. Mid. Res. Inst. Off. Toxic Subs. U.S. EPA, Washington, D.C.

U.S. EPA. 1975b. HCB review report: Fifth 90-day HCB meeting and status of HCB studies.

U.S. EPA. 1976. An ecological study of hexachlorobenzene. EPA-560/6-76-009.

Vos, J.G., et al. 1971. Toxicity of hexachlorobenzene in Japanese quail with special reference to prophyria, liver damage, reproduction, and tissue residues. Toxicol. Appl. Pharmacol. 18: 944.

Weast, R.C. (ed.) 1975. Handbook of Chemistry and Physics. The Chemical Rubber Co., Cleveland, Ohio.

West, W.L. and S.A. Ware. 1977. Preliminary Report. Investigation of Selected Potential Environmental Contaminants: Halogenated Benzenes. Environ. Prot. Agency, Washington, D.C.

Zitko, V. 1971. Polychlorinated biphenyls and organochlorine pesticides in some freshwater and marine fish. Bull. Environ. Contam. Toxicol. 6: 464.

Aquatic Life Toxicology*

INTRODUCTION

This discussion does not cover any dichlorobenzene since they are discussed in a separate criterion document. There is a diversity of toxicological data with numerous species, and there is a consistent direct relationship between toxicity and bioconcentration and degree of chlorination for fish, invertebrate, and plant species. The acute toxicity of hexachlorobenzene is difficult to ascertain since acute mortality for a variety of species appears to occur at or above solubility.

EFFECTS

Acute Toxicity

The 48-hour EC_{50} values reported for Daphnia magna (U.S. EPA, 1978) are (µg/l): chlorobenzene, 86,000; 1,2,4-trichlorobenzene, 50,200; 1,2,3,5-tetrachlorobenzene, 9,710; and pentachlorobenzene, 5,280 (Table 1). The 48-hour EC_{50} value for 1,2,4,5-tetrachlorobenzene was greater than the highest exposure concentration, 530,000 µg/l (Table 5). The 48-hour EC_{50} for three dichlorobenzenes and Daphnia magna ranged from 2,440 to 28,100 µg/l. For Daphnia magna the toxicity of chlorinated benzenes generally tended to increase as the degree of chlorination increased.

No marked difference in sensitivity between fish and invertebrate species is evident from the available data. Pickering and Henderson (1966) reported 96-hour LC_{50} values for goldfish, guppy, and bluegill to be 51,620, 45,530, and 24,000 µg/l, respectively, for chlorobenzene (Table 1).

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

The 96-hour LC_{50} values for chlorobenzene and fathead minnows were 33,930 and 29,120 µg/l in soft water (20 mg/l) and 33,930 µg/l in hard water (360 mg/l) (Table 1). This indicates that hardness does not significantly affect the toxicity of chlorobenzene. U.S. EPA (1978) reported 96-hour LC_{50} values for bluegill exposed to chlorobenzene, 1,2,4-trichlorobenzene, 1,2,3,5-tetrachlorobenzene, 1,2,4,5-tetrachlorobenzene and pentachlorobenzene to be 15,900, 3,360, 6,420, 1,550 and 250 µg/l, respectively. Comparable tests (U.S. EPA, 1978) were conducted with three dichlorobenzenes and the 96-hour LC_{50} values ranged from 4,280 to 5,590 µg/l. Only 1,2,3,5-tetrachlorobenzene is an apparent anomaly in the trend of increasing toxicity with increasing chlorination.

Mysid shrimp, the only saltwater invertebrate species tested, was more sensitive to three of five chlorinated benzenes than the sheepshead minnow and more sensitive to all chlorinated benzenes tested than the freshwater cladoceran, Daphnia magna (Table 1). Chlorobenzene (96-hour LC_{50} = 16,400 µg/l) was the least toxic to mysid shrimp, while pentachlorobenzene (96-hour LC_{50} = 160 µg/l) was the most acutely toxic. As with the freshwater species, and as will be seen with the sheepshead minnow, sensitivity to the chlorinated benzenes (including the dichlorobenzenes) generally increased as chlorination increased.

Toxicity tests with the sheepshead minnow have also been conducted (U.S. EPA, 1978) with five chlorinated benzenes (Table 1). As with the mysid shrimp, all tests were conducted under static conditions and concentrations in water were not measured. Concentrations acutely toxic to this saltwater fish species were relatively high for the lower chlorinated benzenes and toxicity generally increased with increasing chlorination; 96-hour LC_{50} values for sheepshead minnows and dichlorobenzenes (7,440 to 9,660 µg/l) were sightly lower than that for chlorobenzene. The sheepshead minnow was generally more acutely sensitive to the chlorinated benzenes, except for 1,2,4-trichlorobenzene and pentachlorobenzene, than were the freshwater fish species tested similarly (Table 1); 96-hour LC_{50} values for sheepshead minnows and bluegills differed by factors of 1.5 to 6.4. The 96-hour LC_{50} values for sheepshead minnows ranged from 21,400 µg/l for 1,2,4-trichlorobenzene to 830 µg/l for pentachlorobenzene.

Chronic Toxicity

No chronic test has been conducted with any invertebrate species. However, five embryo-larval tests have been conducted with chlorinated benzenes and the fathead minnow and the sheepshead minnow (Table 2). Chronic values for the fathead minnow and 1,2,4-trichlorobenzene have been determined in two studies (U.S. EPA, 1978, 1980). These results provide an acute-chronic ratio of 6.4 (geometric mean of the ratios 10 and 4.1) for this species and 1,2,4-trichlorobenzene (Table 2). The fathead minnow is a little more sensitive to 1,2,3,4-tetrachlorobenzene when tested by the same investigators (U.S. EPA, 1980), with a chronic value of 318 µg/l and an acute-chronic ratio of 3.4 (Table 2).

The chronic values for the sheepshead minnow and 1,2,4-trichlorobenzene and 1,2,4,5-tetrachlorobenzene are 222 and 129 µg/l, respectively (Table 2). The LC_{50} values obtained by the same investigator (U.S. EPA, 1978) are used to calculate the acute-chronic ratios of 96 and 6.5 for 1,2,4-trichlorobenzene and 1,2,4,5-tetrachlorobenzene, respectively (Table 2). The acute-chronic ratio of 96 for the sheepshead minnow and 1,2,4-trichlorobenzene is atypical when compared to the narrow range of ratios for other species and/or chlorinated benzenes of 3.4 to 10.

Plant Effects

Ninety-six-hour EC_{50} tests, using chlorophyll _a_ inhibition and cell number production as measured responses, were conducted with the alga, Selenastrum capricornutum (Table 3). The effects of chlorinated benzenes on this alga generally increased as chlorination increased, but the trend was not smooth. The alga was considerably less sensitive than fish and Daphnia magna with 96-hour EC_{50} values ranging from 6,630 µg/l for pentachlorobenzene to 232,000 µg/l for chlorobenzene.

The saltwater alga, Skeletonema costatum, was less sensitive to the chlorinated benzenes than the mysid shrimp or sheepshead minnow (Table 3). Ninety-six-hour EC_{50} values for growth, based on concentrations of chlorophyll a in culture, were comparable to 96-hour EC_{50} values calculated from cell numbers and, except for chlorobenzene, EC_{50} values for Skeletonema costatum were 3 to 25 times lower than EC_{50} values for the freshwater alga. Those EC_{50} values for the saltwater alga based on chlorophyll a and cell numbers, respectively, are: 343,000 and 341,000 µg/l chlorobenzene; 8,750 and 8,930 µg/l 1,2,4-trichlorobenzene; 830 and 700 µg/l 1,2,3,5-tetrachlorobenzene; 7,100 and 7,320 µg/l 1,2,4,5-tetrachlorobenzene; and 2,230 and 1,980 µg/l pentachlorobenzene.

There are no data reported on effects of chlorinated benzenes on freshwater or saltwater vascular plants.

Residues

Data which are adequate for computing acceptable bioconcentration factors are available for several chlorinated benzenes. After 28-day exposures, the steady-state bioconcentration factors for bluegill (whole body) for pentachlorobenzene, 1,2,3,5-tetrachlorobenzene, and 1,2,4-trichlorobenzene are 3,400, 1,800, and 182, respectively (Table 4). The half-lives for these compounds were between 2 and 4 days for 1,2,3,5-tetrachlorobenzene and 1,2,4-trichlorobenzene and greater than 7 days for pentachlorobenzene (U.S. EPA, 1978). Hexachlorobenzene has also been tested, and the fathead minnow (whole body) bioconcentrated that compound 22,000 times (Table 4).

For three dichlorobenzenes the bioconcentration factors ranged from 60 to 89 (U.S. EPA, 1978); these results are discussed in the criterion document for that group of compounds.

Bioconcentration factors correlate well with an increase in chlorine content. The sequence of measured bioconcentration factors are 72 (mean of dichlorobenzene data), 182 (1,2,4,-trichlorobenzene), 1,800 (1,2,3,5-tetrachlorobenzene), 3,400 (pentachlorobenzene), and 22,000 (hexachlorobenzene) for freshwater species.

Hexachlorobenzene is bioconcentrated from water into tissues of saltwater organisms (Tables 4 and 5). Bioconcentration factors range from 1,964 to 23,000 for fish and shellfish (Parrish, et al. 1974). However, the bioconcentration factors for fish and invertebrate species exposed for only 96 hours probably underestimate steady-state factors for organisms chronically exposed to hexachlorobenzene. Bioconcentration factors for grass shrimp, pink shrimp, and sheepshead minnows exposed to hexachlorobenzene for 96 hours ranged from 1,964 to 4,116 while the bioconcentration factor for pinfish was 15,203 (Table 4). Concentrations of hexachlorobenzene in these whole-body samples were probably not at equilibrium after such a short exposure period; highly chlorinated compounds generally do not reach equilibrium in exposed animals in short exposure periods.

The bioconcentration factor in the flesh of pinfish exposed for 42 days to hexachlorobenzene was 23,000 (Table 4) for the five exposure concentrations tested (0.06 to 5.2 µg/l). Analysis of the concentrations of hexachlorobenzene in pinfish indicates that concentrations after 7 days of exposure were approximately one quarter of the total concentration after 42 days of exposure; concentrations after 42 days of exposure appear to be near equilibrium. Concentrations of hexachlorobenzene in pinfish muscle were reduced only 16 percent after 28 days of depuration; this slow rate is similar to that for DDT in fishes (Parrish, et al. 1974). Since hexachlorobenzene bioconcentrated to high concentrations in all tissues of pinfish and depuration was slow compared to several other organochlorine pesticides (Parrish, et al. 1974), this compound has a high potential for transfer through and retention in aquatic food webs.

Miscellaneous

A variety of data on other adverse effects on freshwater organisms is presented in Table 5. Bioconcentration factors derived from a model ecosystem (Isensee, et al. 1976) ranged from 730 to 9,870 but it could not be determined if these were steady-state results.

Birge, et al. (1979) exposed rainbow trout embryos for 16 days and goldfish and largemouth bass embryos and larvae for up to 4 days post-hatch to chlorobenzene and observed total mortality of the rainbow trout embryos at the lowest measured exposure concentration of 90 µg/l. Hardness did not affect the LC_{50} values for the goldfish (880 and 1,040 µg/l) or the much more sensitive largemouth bass (50 and 60 µg/l).

As mentioned in the introduction, the acute toxicity of hexachlorobenzene is difficult to determine. Tests with a midge, Tanytarsus dissimilis, rainbow trout, fathead minnow, and the bluegill (U.S EPA, 1980) produced no LC_{50} values at concentrations of hexachlorobenzene above what appeared to be its solubility limit.

Summary

In general, the toxicity of the chlorinated benzenes to freshwater organisms increases with increasing chlorination. Chlorobenzene is least toxic with 50 percent effect concentrations for Daphnia magna, goldfish, fathead minnows, guppy, and bluegill in the range of concentrations from 15,900 µg/l to 86,000 µg/l with the cladoceran being a little more resistant than the tested fish species. The dichlorobenzenes, discussed in detail in another document, are slightly more toxic than chlorobenzene. Toxicity reaches its maximum with acute effect concentrations of pentachlorobenzene in the range of 250 µg/l for the bluegill to 5,280 µg/l for *Daphnia magna*. Embryo-larval tests have been conducted with the fathead minnow, and the chronic values are 286 and 705 µg/l for 1,2,4-trichlorobenzene (two tests) and 318 µg/l for 1,2,3,4-tetrachlorobenzene. Acute-chronic ratios from fathead minnow data were 6.4 for 1,2,4-trichlorobenzene and 3.4 for 1,2,3,4-tetrachlorobenzene. A freshwater algal species also was more sensitive to more highly chlorinated benzenes with 96-hour EC_{50} values for chlorophyll *a* in the range of 232,000 µg/l for chlorobenzene to 6,780 µg/l for pentachlorobenzene. The bioconcentration of chlorinated benzenes also increased with increasing chlorination. The whole body bioconcentration factors increased from 182 for 1,2,4-trichlorobenzene to 22,000 for hexachlorobenzene. Acute lethal effects in a midge, rainbow trout, fathead minnow, and bluegill were not observed at concentrations approximating the solubility of hexachlorobenzene.

As with the freshwater toxicity tests with fish and invertebrate species, there was an increase in effects with the more highly chlorinated compounds with at least a one order of magnitude decrease in 96-hour LC_{50} values between chlorobenzene and pentachlorobenzene for the mysid shrimp (16,400 and 160 µg/l) and the sheepshead minnow (10,500 and 830 µg/l). Chronic values for the sheepshead minnow were 222 µg/l for 1,2,4-trichlorobenzene and 129 µg/l for 1,2,4,5-tetrachlorobenzene. A saltwater algal species was more resistant than the fish and invertebrate species, with 96-hour EC_{50} values for chlorophyll *a* in the range of 343,000 µg/l for chlorobenzene to 2,230 µg/l for pentachlorobenzene. Bioconcentration factors for hexachlorobenzene were as high as 23,000 for edible portions of the pinfish.

CRITERIA

The available data for chlorinated benzenes indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 250 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of the more toxic of the chlorinated benzenes to sensitive freshwater aquatic life but toxicity occurs at concentrations as low as 50 µg/l for fish species exposed for 7.5 days.

The available data for chlorinated benzenes indicate that acute and chronic toxicity to saltwater aquatic life occur at concentrations as low as 160 and 129 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Table 1. Acute values for chlorinated benzenes

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	chlorobenzene	86,000	86,000	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	1,2,4-trichlorobenzene	50,200	50,200	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	1,2,3,5-tetrachlorobenzene	9,710	9,710	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, U	pentachlorobenzene	5,280	5,280	U.S. EPA, 1978
Rainbow trout, *Salmo gairdneri*	FT, M	1,2,4-trichlorobenzene	1,500	1,500	U.S. EPA, 1980
Goldfish, *Carassius auratus*	S, U	chlorobenzene	51,620	51,620	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	chlorobenzene	33,930	--	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	chlorobenzene	29,120	—	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S, U	chlorobenzene	33,930	32,200	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	FT, M	1,2,4-trichlorobenzene	2,870	2,870	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	FT, M	1,2,3,4-tetrachlorobenzene	1,070	1,070	U.S. EPA, 1980
Guppy, *Poecilia reticulata*	S, U	chlorobenzene	45,530	45,530	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	chlorobenzene	24,000	—	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S, U	chlorobenzene	15,900	19,500	U.S. EPA, 1978

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
Bluegill, *Lepomis macrochirus*	S, U	1,2,4-trichlorobenzene	3,360	3,360	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,2,3,5-tetrachlorobenzene	6,420	6,420	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	1,2,4,5-tetrachlorobenzene	1,550	1,550	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S, U	pentachlorobenzene	250	250	U.S. EPA, 1978
		SALTWATER SPECIES			
Mysid shrimp, *Mysidopsis bahia*	S, U	chlorobenzene	16,400	16,400	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,2,4-trichlorobenzene	450	450	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,2,3,5-tetrachlorobenzene	340	340	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	1,2,4,5-tetrachlorobenzene	1,480	1,480	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	S, U	pentachlorobenzene	160	160	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	chlorobenzene	10,500	10,500	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,2,4-trichlorobenzene	21,400	21,400	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,2,3,5-tetrachlorobenzene	3,670	3,670	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	S, U	1,2,4,5-tetrachlorobenzene	840	840	U.S. EPA, 1978

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Acute Value (µg/l)	Reference
Sheepshead minnow, *Cyprinodon variegatus*	S, U	pentachloro-benzene	830	830	U.S. EPA, 1978

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*S = static, FT = flow-through, U = unmeasured, M = measured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for chlorinated benzenes

Species	Method*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Fathead minnow, *Pimephales promelas*	ELS	1,2,4-trichlorobenzene	200-410	286	U.S. EPA, 1978
Fathead minnow, *Pimephales promelas*	ELS	1,2,4-trichlorobenzene	499-995	705	U.S. EPA, 1980
Fathead minnow, *Pimephales promelas*	ELS	1,2,3,4-tetrachlorobenzene	245-412	318	U.S. EPA, 1980
		SALTWATER SPECIES			
Sheepshead minnow, *Cyprinodon variegatus*	ELS	1,2,4-trichlorobenzene	150-330	222	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	ELS	1,2,4,5-tetrachlorobenzene	92-180	129	U.S. EPA, 1978

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* ELS = Early life stage

Acute-Chronic Ratio

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Fathead minnow *Pimephales promelas*	1,2,4-trichlorobenzene	2,870	286	10
Fathead minnow, *Pimephales promelas*	1,2,4-trichlorobenzene	2,870	705	4.1
Fathead minnow, *Pimephales promelas*	1,2,3,4-tetrachlorobenzene	1,070	318	3.4
Sheepshead minnow, *Cyprinodon variegatus*	1,2,4-trichlorobenzene	21,400	222	96

Table 2. (Continued)

Acute-Chronic Ratio

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Sheepshead minnow, *Cyprinodon variegatus*	1,2,4,5-tetrachlorobenzene	840	129	6.5

Table 3. Plant values for chlorinated benzenes (U.S. EPA, 1978)

Species	Chemical	Effect	Result (µg/l)
	FRESHWATER SPECIES		
Alga, *Selenastrum capricornutum*	chlorobenzene	Chlorophyll *a* 96-hr EC50	232,000
Alga, *Selenastrum capricornutum*	chlorobenzene	Cell numbers 96-hr EC50	224,000
Alga, *Selenastrum capricornutum*	1,2,4-trichlorobenzene	Chlorophyll *a* 96-hr EC50	35,300
Alga, *Selenastrum capricornutum*	1,2,4-trichlorobenzene	Cell numbers 96-hr EC50	36,700
Alga, *Selenastrum capricornutum*	1,2,3,5-tetrachlorobenzene	Chlorophyll *a* 96-hr EC50	17,200
Alga, *Selenastrum capricornutum*	1,2,3,5-tetrachlorobenzene	Cell numbers 96-hr EC50	17,700
Alga, *Selenastrum capricornutum*	1,2,4,5-tetrachlorobenzene	Chlorophyll *a* 96-hr EC50	52,900
Alga, *Selenastrum capricornutum*	1,2,4,5-tetrachlorobenzene	Cell numbers 96-hr EC50	46,800
Alga, *Selenastrum capricornutum*	pentachlorobenzene	Chlorophyll *a* 96-hr EC50	6,780
Alga, *Selenastrum capricornutum*	pentachlorobenzene	Cell numbers 96-hr EC50	6,630
	SALTWATER SPECIES		
Alga, *Skeletonema costatum*	chlorobenzene	Chlorophyll *a* 96-hr EC50	343,000
Alga, *Skeletonema costatum*	chlorobenzene	Cell numbers 96-hr EC50	341,000

Table 3. (Continued)

Species	Chemical	Effect	Result (µg/l)
Alga, *Skeletonema costatum*	1,2,4-trichlorobenzene	Chlorophyll *a* 96-hr EC50	8,750
Alga, *Skeletonema costatum*	1,2,4-trichlorobenzene	Cell numbers 96-hr EC50	8,930
Alga, *Skeletonema costatum*	1,2,3,5-tetrachlorobenzene	Chlorophyll *a* 96-hr EC50	830
Alga, *Skeletonema costatum*	1,2,3,5-tetrachlorobenzene	Cell numbers 96-hr EC50	700
Alga, *Skeletonema costatum*	1 2,4,5-tetrachlorobenzene	Chlorophyll *a* 96-hr EC50	7,100
Alga, *Skeletonema costatum*	1,2,4,5-tetrachlorobenzene	Cell numbers 96-hr EC50	7,320
Alga, *Skeletonema costatum*	pentachlorobenzene	Chlorophyll *a* 96-hr EC50	2,230
Alge, *Skeletonema costatum*	pentachlorobenzene	Cell numbers 96-hr EC50	1,980

Table 4. Residues for chlorinated benzenes

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
		FRESHWATER SPECIES			
Bluegill, *Lepomis macrochirus*	whole body	1,2,4-trichlorobenzene	182	28	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	whole body	1,2,3,5-tetrachlorobenzene	1,800	28	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	whole body	pentachlorobenzene	3,400	28	U.S. EPA, 1978
Fathead minnow, *Pimephales promelas*	whole body	hexachlorobenzene	22,000	30	U.S. EPA, 1980
		SALTWATER SPECIES			
Pinfish, *Lagodon rhomboides*	edible portion	hexachlorobenzene	23,000*	42	Parrish, et al. 1974

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* Mean concentration factor in 25 muscle samples.

Table 5. Other data for chlorinated benzenes

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Alga, *Chlorella pyrenoidosa*	hexachlorobenzene	3 mos	Growth	1 to 10,000	Geike & Parasher, 1976b
Alga, *Oedogonium cardiacum*	hexachlorobenzene	33 days	Bioconcentration factor = 730	-	Isensee, et al. 1976
Snail, *Helisoma* sp	hexachlorobenzene	33 days	Bioconcentration factor = 1,500	-	Isensee, et al. 1976
Cladoceran, *Daphnia magna*	1,2,4,5-tetrachlorobenzene	48 hrs	LC50	>530,000	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	hexachlorobenzene	30 days	Bioconcentration factor = 910	-	Isensee, et al. 1976
Red swamp craytish, *Procambarus clarki*	hexachlorobenzene	unknown	Mortality	LC50 not reached at 27.3	Laska, et al. 1978
Midge, *Tanytarsus dissimilis*	hexachlorobenzene	48 hrs	Non-lethal at approx. saturation	57	U.S. EPA, 1980
Rainbow trout (embryo), *Salmo gairdneri*	chlorobenzene	16 days	100% mortality	90	Birge, et al. 1979
Rainbow trout, *Salmo gairdneri*	pentachlorobenzene	144 hrs	LC50	258	U.S. EPA, 1980
Rainbow trout, *Salmo gairdneri*	hexachlorobenzene	96 hrs	Non-lethal at approx. saturation	80	U.S. EPA, 1980
Rainbow trout, *Salmo gairdneri*	hexachlorobenzene	96 hrs	Estimated steady state bioconcentration factor = 7,800	-	Neely, et al. 1974
Atlantic salmon, *Salmo salar*	hexachlorobenzene	48 hrs	Bioconcentration factor = 690	-	Zitko & Hutzinger, 1976
Goldfish (embryo-larval), *Carassius auratus*	chlorobenzene	8 days	LC50 at 50 mg/l hardness	880	Birge, et al. 1979

Table 5. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Goldfish (embryo-larval), *Carassius auratus*	chlorobenzene	8 days	LC50 at 200 mg/l hardness	1,040	Birge, et al. 1979
Fathead minnow, *Pimephales promelas*	hexachlorobenzene	4 days	Non-lethal at approx. saturation	4.8	U.S. EPA, 1980
Channel catfish, *Ictalurus punctatus*	hexachlorobenzene	8 days	Bioconcentration factor = 9,870	-	Isensee, et al. 1976
Mosquitofish, *Gambusia affinis*	hexachlorobenzene	3 days	Bioconcentration factor = 1,580	-	Isensee, et al. 1976
Bluegill, *Lepomis macrochirus*	hexachlorobenzene	4 days	Non-lethal at approx. saturation	78	U.S. EPA, 1980
Largemouth bass (embryo-larval), *Micropterus salmoides*	chlorobenzene	7.5 days	LC50 at 50 mg/l hardness	50	Birge, et al. 1979
Largemouth bass (embryo-larval), *Micropterus salmoides*	chlorobenzene	7.5 days	LC50 at 200 mg/l hardness	60	Birge, et al. 1979
Largemouth bass, *Micropterus salmoides*	hexachlorobenzene	10 and 15 days	No mortality	10 and 26	Laska, et al. 1978
		SALTWATER SPECIES			
Protozoan, *Tetrahymena pyriformis*	hexachlorobenzene	10 days	Decrease growth	1	Geike & Prasher, 1976
Grass shrimp, *Palaemonetes pugio*	hexachlorobenzene	96 hrs	Mean bioconcentration factor = 4,116	-	Parrish, et al. 1974
Pink shrimp, *Penaeus duorarum*	hexachlorobenzene	96 hrs	Mean bioconcentration factor = 1,964	-	Parrish, et al. 1974
Pink shrimp, *Penaeus duorarum*	hexachlorobenzene	96 hrs	33% mortality during exposure to 25 µg/l	-	Parrish, et al. 1974

Table 5. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Sheepshead minnow, *Cyprinodon variegatus*	hexachlorobenzene	96 hrs	Mean bioconcentration factor = 2,254	-	Parrish, et al. 1974
Pinfish, *Lagodon rhomboides*	hexachlorobenzene	96 hrs	Mean bioconcentration factor = 15,203	-	Parrish, et al. 1974

REFERENCES

Birge, W.J., et al. 1979. Toxicity of organic chemicals to embryo-larval stages of fish. EPA-560/11-79-007. U.S. Environ. Prot. Agency. 69 p.

Geike, F. and C.D. Parasher. 1976a. Effect of hexachlorobenzene (HCB) on growth of *Tetrahymena pyriformis*. Bull. Environ. Contam. Toxicol. 16: 347.

Geike, F. and C.D. Parasher. 1976b. Effect of hexachlorobenzene on some growth parameters of *Chlorella pyrenoidosa*. Bull. Environ. Contam. Toxicol. 15: 670.

Isensee, A.R., et al. 1976. Soil persistence and aquatic bioaccumulation potential of hexachlorobenzene (HCB). Jour. Agric. Food Chem. 24: 1210.

Laska, A.L., et al. 1978. Acute and chronic effects of hexachlorobenzene and hexachlorobutadiene in Red Swamp Crayfish (*Procambarus clarki*) and selected fish species. Toxicol. Appl. Pharmacol. 43: 1.

Neely, W.B., et al. 1974. Partition coefficient to measure bioconcentration potential of organic chemicals in fish. Environ. Sci. Tech. 8: 1113.

Parrish, P.R., et al. 1974. Hexachlorobenzene: Effects on several estuarine animals. *In*: Proc. 28th Annu. Conf. S.E. Assoc. Game Fish Comm. p. 179.

Pickering, Q.H. and C. Henderson. 1966. Acute toxicity of some important petrochemicals to fish. Jour. Water Pollut. Control Fed. 38: 1419.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

U.S. EPA. 1980. Unpublished laboratory data. Environmental Research Laboratory - Duluth.

Zitko, V. and O. Hutzinger. 1976. Uptake of chloro- and bromobiphenyls, hexachloro- and hexabromobenzene by fish. Bull. Environ. Contam. Toxicol. 16: 665.

MONOCHLOROBENZENE

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Monochlorobenzene (MCB) is used industrially both as a synthetic intermediate and as a solvent. As a synthetic intermediate, it is primarily used in the production of phenol, DDT and aniline. Because it is noncorrosive, it has technological use as a solvent for a large number of compounds in the manufacture of adhesives, paints, polishes, waxes, diisocyanates, pharmaceuticals and natural rubber.

Data derived from U.S. International Trade Commission reports show that between 1966 and 1975, the U.S. annual production of MCB decreased by 50 percent from approximately 600 million pounds to approximately 300 million pounds (U.S. EPA, 1977). It is, as expected from its structure, lipophilic and hydrophobic, its solubility in water being about 100 parts per million. The log of the octanol to water partition coefficient for MCB is 2.83. Monochlorobenzene also has a relatively high vapor pressure (9 torr at 20°C). As will be seen from the next section, this is an important consideration in estimating the likely retention of MCB in surface waters.

EXPOSURE

Ingestion from Water

Based on the vapor pressure, water solubility, and molecular weight of chlorobenzene, Mackay and Leinonen (1975) estimated the half-life of evaporation from water for MCB to be 5.8 hours as compared to 4.8 hours for benzene and 73.9 hours for DDT.

MCB has been detected in ground water, "uncontaminated" upland water, and in waters contaminated either by industrial, municipal, or agricultural waste. It has been identified in textile plant effluents (Erisman and Goldman, 1975). Table 1 consists of a compilation of data from other EPA reports and shows the results of various water surveys as related to MCB. Considering the volatile nature of MCB, these data should be considered from a point of view of gross estimate of exposure. For example, in the analysis of the water for Lawson's Fork Creek, South Carolina, the range indicated is the result of two analyses four days apart (U.S. EPA, 1977). The presence of MCB at other sites has been demonstrated qualitatively by volatile organic analysis. It has been detected in "uncontaminated" upland water in Seattle, Wash., (Erisman and Goldman, 1975) and in raw water contaminated with agricultural runoff in Ottumwa, Iowa and Grand Falls, North Dakota (U.S. EPA, 1977). Some information is available which might give insight as to the source of contamination. For example, it has been estimated that during the manufacture of MCB, 800 mg escape into column water streams for every kg manufactured. Another 4 g of MCB per kg manufactured is recovered from fractionating columns for land disposal (U.S. EPA, 1977).

Ingestion from Food

Lu and Metcalf (1975) determined the ecological magnification of MCB in various aquatic species. Their data are shown in Table 2. For the purposes of comparison, the ecological magnification of aldrin and DDT in mosquito fish was 1,312 and 16,960, respectively.

TABLE 1

Examples of Occurrence of Monochlorobenzene

Location	Source	Concentration (µg/l)
Miami, FL	Ground water	1.0
Philadelphia, PA	Raw water contaminated with municipal waste	0.1
Cincinnati, OH	Raw water contaminated with industrial discharge	0.1 - 0.5
New York, NY	"Uncontaminated" upland water	4.7
Lawrence, MA	Raw water contaminated with industrial discharge	0.12
Terrebone Parish, LA	Raw water contaminated with municipal waste	5.6
Lawsons Fork Creek, SC	Industrial discharge	8.0 - 17.0
Coosa River, GA	Municipal	27.0

*Source: U.S. EPA, 1975; 1977.

TABLE 2
Ecological Magnification of Monochlorobenzene in Various Aquatic Organisms*

Species	Ecological Magnification *($C_{organism}/C_{H_2O}$)
Mosquito fish _Gambusia affinis_	645
Mosquito larvae _Culex quinquifasciatus_	1292
Snails _Physa_	1313
Daphnia _Daphnia magna_	2789
Algae _Oedogonium cardiacum_	4185

*Source: Lu and Metcalf, 1975; U.S. EPA, 1977.

Further data by Lu and Metcalf (1975) indicate that MCB resists biodegradation. They determined the biodegradability index (BI) which was defined as the ratio of polar products of degradation to the nonpolar products. For MCB, the BI ranged from 0.014 to 0.063 in the organisms shown in Table 2. The low value for BI was similar to that seen for DDT and aldrin. For example, in mosquito fish the BI for MCB was 0.014, for DDT it was 0.012 and for aldrin it was 0.015.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals, to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state bioconcentration factor (BCF) is available for chlorobenzene, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al., 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol-water partition coefficient (P). Based on an average measured log P value of 2.49 (Hansch and Leo, 1979), the steady-state bioconcentration factor for chlorobenzene is estimated to be 26.1. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average bioconcentration factor for chlorobenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 26.1 x 0.395 = 10.3.

Inhalation

No data have been found which deal with exposure to MCB by air outside of the industrial working environment. The information concerning the industrial exposure of workers has come primarily from eastern European sources and is tabulated in Table 3. In addition to that information, Girard, et al. (1969) reported on a case of an elderly female who was exposed to a glue, containing 0.07 percent MCB, for a period of six years (see Special Groups at Risk).

Dermal

Pertinent data concerning the dermal exposure of MCB could not be located in the available literature.

TABLE 3

Recorded Industrial Exposures to Monochlorobenzene

Plant Activity	Concentration of MCB (mg/l)	Reference
Manufacture of DDT	0.020 - average 0.300 - highest	Gabor and Raucher, 1960
Manufacture of monuron	0.001 - 0.01	Levina, et al. 1966
	0.004 - 0.01	Stepanyan, 1966

Summary and Conclusions

Water is a documented source of environmental exposure to MCB. Because of the short half-life of MCB in water, it would be relatively difficult to monitor human exposure unless multiple sampling was done. Compared to substances such as DDT, the accumulation of MCB within the food chain is limited; however, even this accumulation tends to magnify the possible human exposure to MCB via discharge into water.

PHARMACOKINETICS

Absorption

There is little question, based on human effects and mammalian toxicity studies, that MCB is absorbed through the lungs and from the gastrointestinal tract (U.S. EPA, 1977). Based on what is known about congeners, it is also probably absorbed from the surface of the skin.

Distribution

Because MCB is highly lipophilic and hydrophobic, it would be expected that it would be distributed throughout total body water space, with body lipid providing a deposition site. The data available on the related halobenzene, bromobenzene, show this to be the case (Reid, et al. 1971). Barring some abnormal kinetic pattern, it would also be expected that redistribution from tissue sites would reflect plasma decay rates. Again, with bromobenzene this was the case, the plasma $t_{(1/2)}$ being 5.8 hours and the $t_{(1/2)}$ for fat being 6.2 hours.

Metabolism

Metabolism of MCB has been studied in a number of laboratories. Hydroxylation occurs para to the chloride via an NADPH-cytochrome P-448 dependent microsomal enzyme system. Further hydroxylation then occurs to form the corresponding catechol compound. The diphenolic derivative is a predominant form, quantitatively, in comparison to the monophenolic compounds. Various conjugates of these phenolic derivatives are the primary excretory products (Lu, et al. 1974). The conjugates are formed by microsomal enzymes, in this case, the NADPH-cytochrome P-450 dependent system. However, it would appear that the rate-limiting step in metabolism of MCB is the initial hydroxylation of the ring. There are some differences in the nature of the conjugates, depending upon the animal species studied. Williams, et al. (1975) found that among 13 species of nonhuman mammals, 21 to 65 percent of excreted radioactivity from the administration of ^{14}C-MCB was present in the urine as p-chlorophenylmercapturic acid. The output of this conjugate in man was only 16 percent of the administered dose. Williams (1959) also reported that about 27 percent of MCB administered to the rabbit was expired unchanged in the air over a 1 to 2 day period; 47 percent of the dose was excreted as glucuronic acid or sulfate conjugate and 25 percent as mercapturic acid conjugate. This accounts for the total dose and would imply that very little is excreted unchanged. This would be expected, as the lipophilic nature of MCB would predict that it would be almost totally reabsorbed by the renal tubules such that its decay from the plasma would rely totally on metabolism and on ventilatory excretion.

The ease with which MCB is eliminated via the lungs or metabolized would predict that its bioaccumulation potential is somewhat limited. Varshavskaya (1968) found that when MCB was administered to rats at 0.001 mg/day for nine months, the coefficient of accumulation was 1.25. This would mean that accumulation is somewhat less than if the exposure level is kept constant. For example, if a single dose were taken every 24 hours and this resulted in a total body accumulation of 1.25 x the dose, the $t_{(1/2)}$ would be calculated to be approximately 11 hours. This would suggest that in the rat, upon exposure to a constant dose, the maximum body concentration is reached in about two days. The same numbers cannot be applied to man because of differences in organ clearance rates, but relatively speaking it would be expected that equiblibrium would be reached in a short time from an environmental point of view and that prolonged exposure to constant levels in the environment would not be expected to result in continuous accumulation.

Evidence has been accumulating which implies that the metabolism of halogenated benzene compounds results in the formation of toxic intermediates. Brodie, et al. (1971) pretreated animals with phenobarbital to stimulate the activity of drug metabolizing enzymes in the liver. This treatment potentiated liver necrosis induced by halogenated aromatic compounds (of which monobromobenzene was the primary example). This is apparently related to the formation of metabolites capable of forming complexes with cellular ligands. The covalent binding of the metabolites of halogenated benzene derivatives with protein has been correlated with the ability of these compounds to induce hepatic necrosis (Reid, et al. 1971, 1973; Reid and Krishna, 1973). Oesch, et al. (1973) have reported that rats pretreated with 3-methylcholanthrene are protected from MCB-evoked hepatotoxicity. This was ascribed to the modification of a coupled monooxygenase epoxidehydrase system (Oesch, et al. 1973). Carlson and Tardiff (1976) reported that the oral administration of 10 to 40 mg/day of MCB to rats for 14 days induced a variety of microsomal enzymes which metabolize foreign organic compounds including benzpyrenehydroxylase. Cellular toxicity, including carcinogenic and mutagenic activity, may be related to the formation of highly active metabolic intermediates such as epoxides. In this connection, Kohli, et al. (1976) have suggested that the metabolism of MCB occurs via arene oxide intermediates as shown in Figure 1.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The acute toxic effects of MCB were quantitatively similar in some cases to chlorinated hydrocarbons such as carbon tetrachloride. The oral LD_{50} of monochlorobenzene in the rat is approximately 3 g/kg. When administered by subcutaneous injection, the LD_{50} increases by about 25 percent. Von Oettingen (1955) found that large doses of MCB (7 to 8 g/kg subcutaneously) were fatal in a few hours as a result of CNS depression. When the dose utilized was 4 to 5 g/kg, death occurred after a few days and

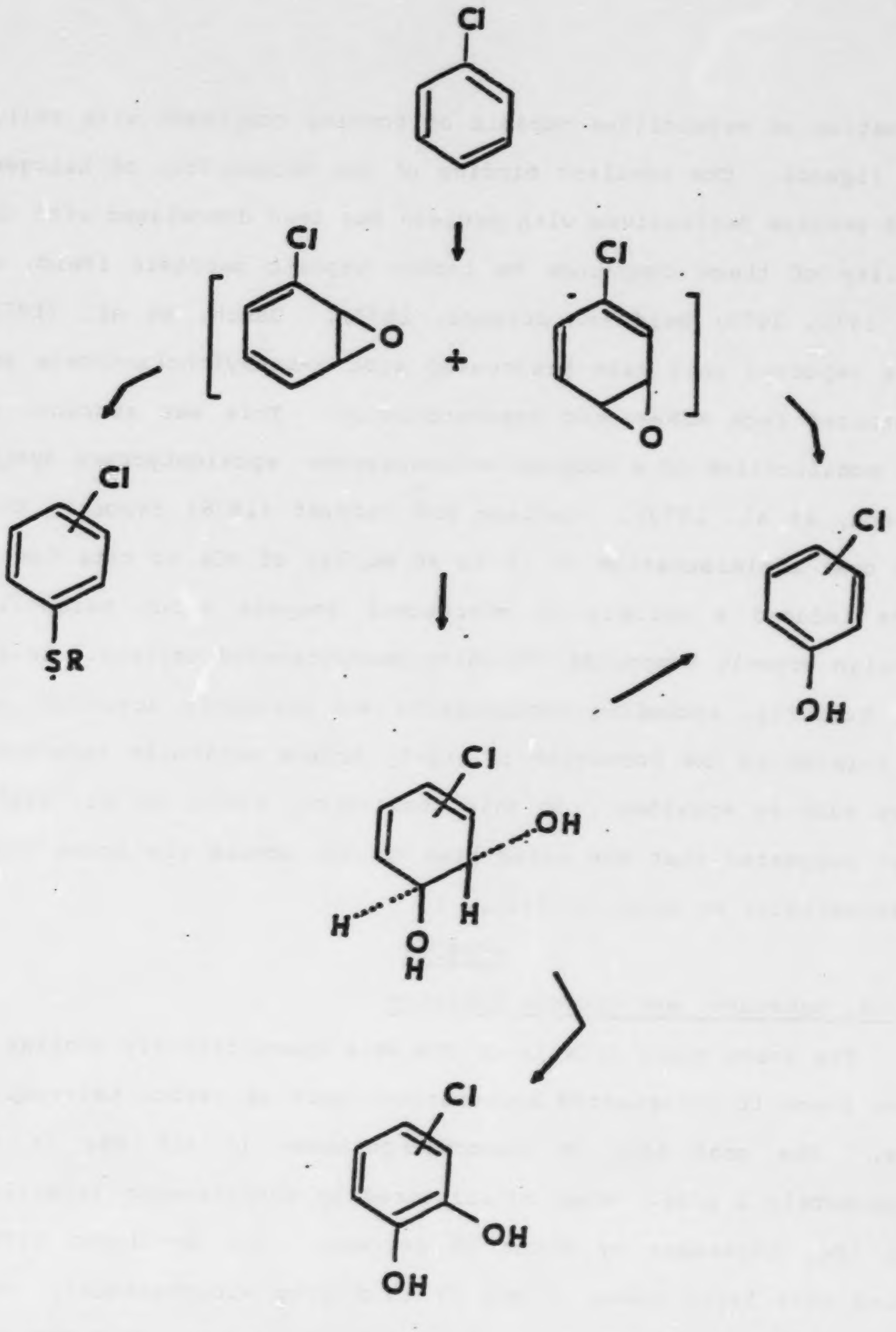
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FIGURE 1

Proposed Route for Biotransformation of Monochlorobenzene Via Arene Oxides
Source: Kohli, et al. 1976

resulted from hepatic and/or renal necrosis. Vecerek, et al. (1976) found the oral LD_{50} of MCB in rats to be 3.4 g/kg. At this dose, the animals died after about seven days and showed signs of a number of metabolic disturbances including elevated levels of SGOT, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, and decreased levels of glycogen phosphorylase and blood sugars. Yang and Peterson (1977) administered MCB at 5 mmol/kg (about 563 mg/kg) intraperitoneally to male rats and found an increase in the flow of bile duct pancreatic fluid.

Data on the subchronic and chronic toxicity of MCB are sparse and somewhat contradictory. Lecca-Radu (1959) administered MCB by inhalation to rats and guinea pigs for periods up to one year in doses which did not affect the liver or the kidney but did modify erythrocyte carbonic anhydrase and leukocyte indolephenol oxidase activities. Knapp, et al. (1971) administered MCB orally by capsule to dogs in doses of 27.2, 54.5, and 272.5 mg/kg/day five days a week over a 90-day period. Four of eight of the animals in the high dose group died after 14 to 21 daily doses. Clinical studies prior to death revealed an increase in immature leukocytes, low blood sugar, elevated SGPT and alkaline phosphatase and, in some dogs, increases in total bilirubin and total cholesterol. "Gross and/or microscopic pathological changes" were seen in the liver, kidneys, gastrointestinal mucosa, and hematopoietic tissue of the dogs which died and, less extensively, in the dogs which were sacrificed after 65 or 66 daily doses. No consistent signs of MCB toxicity were seen in dogs in the intermediate and low levels.

MCB was given to rats by diet at doses of 12.5, 50 and 250 mg/kg/day for a period of 93 to 99 days. Growth was retarded in male rats in the high dose group. There was an increase in liver and kidney weight for rats in the high and intermediate levels. This was not accompanied by any "histopathological" findings (Knapp, et al. 1971).

The toxicity of MCB following exposure by inhalation and by oral administration has been studied by the Dow Chemical Company (Irish, 1963). Rats, rabbits and guinea pigs were exposed seven hours a day, five days a week, for a total of 32 exposures over a period of 44 days at concentrations of 200, 475, and 1,000 ppm. The response of the animals in the high dose group was characterized by "histopathological changes" in the lungs, liver and kidneys. In the middle dose group, there was an increase in liver weight and a slight liver "histopathology". In the low dose group, no apparent effects were observed. In none of the groups was a hematological change seen. MCB was administered orally to rats five days a week for a total of 137 doses over 192 days, in dose groups of 14.4, 144 and 228 mg/kg. In the middle and high dose groups there were significant increases in liver and kidney weight and some "histopathological changes" in the liver. Blood and bone marrow were normal in all animals (Irish, 1963).

Rimington and Ziegler (1963), citing the widespread outbreak of human cutaneous porphyria in Turkey in 1959 apparently caused by wheat treated with hexachlorobenzene fungicide, examined a series of chlorinated benzene compounds in rats with regard to experimental porphyria. MCB at an oral dose of 1140 mg/kg for five days increased the excretion of urinary coproporphyrin, porphorobilinogen, and delta-aminolevulinic acid. Some hair loss was also observed due to follicular hyperkeratosis.

A study by Varshavskaya (1968) describes the central nervous system (CNS), liver and hematopoietic system changes in seven male rats per group which received oral doses of 0.1 mg/kg to 0.001 mg/kg MCB for a period of nine months. This report indicates that doses of 0.001 mg/kg MCB for seven months affected the CNS of rats and that similar effects resulted from similar o-dichlorobenzene dosages. However, these results are somewhat unexpected in light of other studies in the literature. For example, Hollingsworth, et al. (1956) reported similar results from an experiment with o-dichlorobenzene which differed by over three orders of magnitude from those of the Varshavskaya (1968) study. This discrepancy in o-dichlorobenzene results leaves the MCB results of the Varshavskaya study open to question.

Synergism and/or Antagonism

In general, the halogenated benzenes appear to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides, and other xenobiotics. Exposure to monochlorobenzene could, therefore, result in decreased pharmacologic and/or toxicologic activity of numerous compounds. Frequently, chemical agents are metabolized to more active or toxic "reactive" intermediates. In this event, exposure to monochlorobenzene would result in enhanced activity and/or toxicity of these agents.

Teratogenicity, Mutagenicity, and Carcinogenicity

There have been no studies conducted to evaluate the teratogenic, mutagenic or carcinogenic potentials of MCB.

CRITERION FORMULATION

Existing Guidelines and Standards

The Threshold Limit Value (TLV) for MCB as adopted by the American Conference of Governmental Industrial Hygienists (ACGIH, 1971) is 75 ppm (350 mg/m^3). The American Industrial Hygiene Association Guide (1964) considered 75 ppm to be too high. The recommended maximal allowable concentrations in air in other countries are: Soviet Union, 10 ppm; Czechoslovakia, 43 ppm; and Romania, 0.05 mg/l. The latter value for Romania was reported by Gabor and Raucher (1960) and is equivalent to 10 ppm.

Current Levels of Exposure

MCB has been detected in water monitoring surveys of various U.S. cities (U.S. EPA, 1975; 1977) as was presented in Table 1. Levels reported were: ground water - 1.0 µg/l; raw water contaminated by various discharges - 0.1 to 5.6 µg/l; upland water - 4.7 µg/l; industrial discharge - 8.0 to 17.0 µg/l; and municipal water - 27 µg/l. These data show a gross estimate of possible human exposure to MCB through the water route.

Evidence of possible exposure from food ingestion is indirect. MCB is stable in water and thus can be bioaccumulated by edible fish species.

The only data concerning exposure to MCB via air are from the industrial working environment. Reported industrial exposures to MCB are 0.02 mg/l (average value) and 0.3 mg/l (highest value) (Gabor and Raucher, 1960); 0.001 to 0.01 mg/l (Levina, et al. 1966); and 0.004 to 0.01 mg/l (Stepanyan, 1966).

Special Groups at Risk

The major group at risk of MCB intoxication are individuals exposed to MCB in the workplace. Girard, et al. (1969) reported the case of an elderly female exposed to a glue containing 0.07 percent MCB for a period of six years. She had symptoms of headache, irritation of the eyes and the upper respiratory tract, and was diagnosed to have medullary aplasia. Smirnova and Granik (1970) reported on three adults who developed numbness, loss of consciousness, hyperemia of the conjunctiva and the pharynx following exposure to "high" levels of MCB. Information concerning the ultimate course of these individuals is not available. Gabor, et al. (1962) reported on individuals who were exposed to benzene, chlorobenzene, and vinyl chloride. Eighty-two workers examined for certain biochemical indices showed a decreased catalase activity in the blood and an increase in peroxidase, indophenol oxidase, and glutathione noted levels. Dunaeveskii (1972) reported on the occupational exposure of workers exposed to the chemicals involved in the manufacture of chlorobenzene at limits below the allowable levels. After over three years, cardiovascular effects were noted as pain in the area of the heart, bradycardia, irregular variations in electrocardiogram, decreased contractile function of myocardium, and disorders in adaptation to physical loading. Filatova, et al. (1973) reported on the prolonged exposure of individuals involved in the production of diisocyanates to factory air which contained MCB as well as other chemicals. Diseases noted include bronchitis, sinus arrhythmia, tachycardia, arterial dystrophy, and anemia tendencies. Petrova and Vishnevskii (1972) studied the course of pregnancy and deliveries in women exposed to air in a varnish manufacturing factory where the air contained three times the maximum permissible level of MCB but also included toluene, ethyl chloride, butanol, ethyl bromide, and orthosilisic acid ester. The only reported significant adverse effect of this mixed exposure was toxemia during pregnancy.

Basis and Derivation of Criterion

There is no information in the literature which indicates that monochlorobenzene is, or is not, carcinogenic. There is enough evidence to suggest that MCB causes dose-related target organ toxicity, although the data are lacking an acceptable chronic toxicity study. There is little, if any, usable human exposure data primarily because the exposure was not only to MCB but to other compounds of known toxicity.

A no-observable-adverse effect level (NOAEL) for derivation of the water quality criterion can be extracted from the information in the studies by Knapp, et al. (1971) and Irish (1963). These are 27.25 mg/kg/day for the dog (the next highest dose was 54.5 mg/kg and showed an effect); 12.5 mg/kg/rat from the Knapp study (the next highest dose was 50 mg/kg and showed an effect); and 14.5 mg/kg/rat from the Irish study (the next highest dose was 144 mg/kg and showed an effect). When toxic effects were observed at higher doses, the dog was judged to be somewhat more sensitive than rats. The duration of the study by Irish (1963) was six months, which was twice as long as the Knapp study of two species (rat, dog). Since the Knapp and Irish studies appear to give similar results and since there are no chronic toxicity data on which to rely, the NOAEL level, 14.4 mg/kg for six months, from the longest term study (Irish, 1963) is used to calculate the acceptable daily intake (ADI).

Considering that there are relatively little human exposure data, that there are no long-term animal data, and that some theoretical questions, at least, can be raised on the possible effects of chlorobenzene on blood-forming tissue an uncertainty factor of 1,000 is used. From this (ADI) can then be calculated as follows:

$$\text{ADI} = \frac{70 \text{ kg} \times 14.4 \text{ mg/kg}}{1{,}000} = 1.008 \text{ mg/day}$$

The average daily consumption of water was taken to be two liters and the consumption of fish and shellfish to be 0.0065 kg daily. A bioconcentration factor of 10.3 was utilized. This is the value reported by the Duluth EPA Laboratories (see Ingestion from Food section). The following calculation results in a criterion based on the available toxicologic data:

$$\frac{1.008}{2 + (10.3 \times 0.0065)} = 488 \text{ µg/l}$$

Varshavskya (1968) has reported the threshold concentration for odor and taste of MCB in reservoir water. The specific methods whereby the organoleptic data were obtained are not detailed in this report. The only statement made was that different methods provided similar estimates of threshold concentrations. The reported olfactory and gustatory threshold was found to be 10 to 20 µg/l. A value of 20 µg/l is about 4.5 percent of the possible criterion calculated above. It is, however, approximately 17 times greater than the highest concentrations of MCB measured in survey sites (see Table 1). Since water of disagreeable taste and odor has significant influence on the quality of life and, thus, is related to health, it would appear that the organoleptic level of 20 µg/l should be the recommended criterion.

REFERENCES

American Conference of Governmental Industrial Hygienists. 1971. Documentation of the Threshold Limit Values for Substances in Workroom Air. 3rd ed.

American Industrial Hygiene Association. 1964. Chlorobenzene. Am. Ind. Hyg. Assoc. Jour. 25: 97.

Brodie, B.B., et al. 1971. Possible mechanism of liver necrosis caused by aromatic organic compounds. Proc. Natl. Acad. Sci. 68: 160.

Carlson, G.P. and R.G. Tardiff. 1976. Effect of chlorinated benzenes on the metabolism of foreign organic compounds. Toxicol. Appl. Pharmacol. 36: 383.

Dunaeveskii, G.A. 1972. Functional condition of circulatory organs in workers employed in the production of organic compounds. Gig. Tr. Prof. Zabol. 16: 48.

Erisman, H. and M. Goldman. 1975. Identification of organic compounds in textile plant effluents. Presented at the First Chemical Congress of the North American Continent, Mexico City, Mexico, November 30 - December 5.

Filatova, V.S., et al. 1973. Industrial hygiene and pathology in production and use of diisocyanates. Profil. Trarmatizma Prof. Zabol., Lech. Traum. 219.

Gabor, S. and K. Raucher. 1960. Studies on the determination of the maximum permissible concentrations of benzene and monochlorobenzene. Jour. Hyg. Epidemiol. Microbiol. Immunol. 4: 223.

Gabor, S., et al. 1962. Certain biochemical indexes of the blood in workers exposed to toxic substances (benzene, chlorobenzene, vinyl chloride). Prom. Toxikol. i Klin. Prof. Zabol. Khim. Etiol. SB 221.

Girard, R., et al. 1969. Serious blood disorders and exposure to chlorine derivatives of benzene. (A report of 7 cases.) Jour. Med. Lyon. 50: 771.

Hansch, C. and J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley Interscience, New York. p. 339.

Hollingsworth, R.L., et al. 1956. Toxicity of paradichlorobenzene: Determination on experimental animals and human subjects. AMA Arc. Ind. Health. 14: 138.

Irish, D.D. 1963. Halogenated Hydrocarbons: II. Cyclic. In: F.A. Patty (ed.), Industrial Hygiene and Toxicology, Vol. II, 2nd ed. Interscience, New York. p. 1333.

Knapp, W.K. Jr., et al. 1971. Subacute oral toxicity of monochlorobenzene in dogs and rats. Toxicol. Appl. Pharmacol. 19: 393.

Kohli, I., et al. 1976. The metabolism of higher chlorinated benzene isomers. Can. Jour. Biochem. 54: 203.

Lecca-Radu, M. 1959. Modifications of blood carbonic anhydrase and indophenol oxidase in chronic benzene and monochlorobenzene intoxication. Igiena: 231.

Levina, M.M., et al. 1966. Issues concerning sanitary working conditions and the state of health of those workers in the field of monuron production. Gig. Tr. Prog. Zabol. 11: 54.

Lu, A.Y.H., et al. 1974. Liver microsomal electron transport systems. III. Involvement of cytochrome b_5 in the NADH-supported cytochrome P^5-450 dependent hydroxylation of chlorobenzene. Biochem. Biphys. Res. Comm. 61: 1348.

Lu, P.Y. and R.L. Metcalf. 1975. Environmental fate and biodegradability of benzene derivatives as studied in a model aquatic ecosystem. Environ. Health Perspect. 10: 269.

Mackay, D. and P.J. Leinonen. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol. 9: 1178.

Oesch, F., et al. 1973. Induction activation and inhibition of epoxide hydrase. Anomalous prevention of chlorobenzene-induced hepatotoxicity by an inhibitor of epoxide hydrase. Chem. Biol. Interact. 6: 189.

Petrova, N.L. and A.A. Vishnevskii. 1972. Course of pregnancy and deliveries in women working in the organosilicon varnish and enamel industries. Nauch Jr. Incutsk. Med. Inst. 115: 102.

Reid, W.D. and G. Krishna. 1973. Centrolobular hepatic necrosis related to covalent binding of aromatic hydrocarbons. Exp. Molec. Pathol. 18: 80.

Reid, W.D., et al. 1971. Bromobenzene metabolism and hepatic necrosis. Pharmacol. 6: 41.

Reid, W.D., et al. 1973. Metabolism and binding of aromatic hydrocarbons in the lung; relationship to experimental bronchiolar necrosis. Am. Rev. Resp. Dis. 107: 539.

Rimington, C. and G. Ziegler. 1963. Experimental porphyria in rats induced by chlorinated benzenes. Biochem. Pharmacol. 12: 1387.

Smirnova, N.A. and N.P. Granik. 1970. Remote consequences of acute occupational poisoning by some hydrocarbons and their derivatives. Gig. Truda. Prof. Zabol. 5: 50.

Stepanyan, L.K. 1966. Combined effect of chlorobenzene ethyl cellosolve and high temperature on workers. Mater. Itogovoi. Nauch. Konf. Vop. Gig. Tr. Prof. Khim. Gornorud. Prom., 3rd. 47.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Rep. to Congress. EPA 560/4-75-003.

U.S. EPA. 1977. Investigation of selected potential environmental contaminants: Halogenated benzenes. EPA 560/2-77-004.

U.S. EPA. 1980. Seafood Consumption Data Analysis. Stanford Research Institute International, Menlo Park. Calif. Final rep., Task II. Contract No. 68-01-3887.

U.S. International Trade Commission. 1966. Synthetic organic chemicals: U.S. production and sales. U.S. Government Printing Office, Washington, D.C.

U.S. International Trade Commission. 1975. Synthetic organic chemicals: U.S. production and sales. U.S. Government Printing Office, Washington, D.C.

Varshavskaya, S.P. 1968. Comparative toxicological characteristics of chlorobenzene and dichlorobenzene (ortho-and-para-isomers) in relation to the sanitary protection of water bodies. (Rus. trans.) Hyg. San. 33: 10.

Vecerek, B., et al. 1976. Xenobiochemical characteristics of chlorobenzene. Bratisl. Lek. Listy. 65: 9.

Veith, G.D. 1980. Memorandum to C.E. Stephan. U.S. EPA. April 14.

Veith, G.D., et al. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. Jour. Fish. Res. Board Can. 36: 1040.

von Oettingen, W.F. 1955. The Halogenated Aromatic Hydrocarbons. In: The Halogenated Aliphatic, Olefinic, Cyclic, Aromatic and Aliphatic Aromatic Hydrocarbons, Including the Halogenated Insecticides, Their Toxicity and Potential Dangers. U.S. Dept. Hlth. Edu. Wel. 414: 283.

Williams, R.T. 1959. The Metabolism of Halogenated Aromatic Hydrocarbons. In: Detoxication Mechanisms. 2nd ed. John Wiley and Sons, New York. p. 237.

Williams, R.T., et al. 1975. Species Variation in the Metabolism of Some Organic Halogen Compounds. In: A.D. McIntyre and C.F. Mills (eds.), Ecological and Toxicological Research. Plenum Press, New York.

Yang, K.H. and R.E. Peterson. 1977. Differential effects of halogenated aromatic hydrocarbons on pancreatic excretory function in cats. Fed. Proc. 36: 356.

TRICHLOROBENZENES

Mammalian Toxicology and Human Health Effects

INTRODUCTION

There are three isomers of trichlorobenzene (TCB): 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene and 1,3,5-trichlorobenzene. Of the three, 1,2,4-TCB is the most economically important (U.S. EPA, 1977). It is used as a dye carrier in the application of dyes to polyester materials, as an intermediate in the synthesis of herbicides, as a flame retardant, and for other functional uses. The U.S. production of 1,2,4-trichlorobenzene in 1973 was over 28 million pounds (U.S. International Trade Commission, 1975). A mixture of the three isomers is used as a solvent, a lubricant, and as a dielectric fluid. The 1,2,3 and 1,3,5-TCB isomers as individual compounds are primarily used as intermediates in chemical synthesis. TCBs are most probably intermediates in the mammalian metabolism of lindane (Kujawa, et al. 1977).

EXPOSURE

Ingestion from Water

Table 1 shows data from monitoring the various water sites. These data suggest the possibility of TCB contamination of the drinking water. In a report (U.S. EPA, 1975) in which the sample site was not identified, the highest reported concentration of trichlorobenzene in drinking water was 1.0 µg/l.

Ingestion from Food

Whereas the bioaccumulation of some of the other members of the chlorinated benzene series has been studied with regard to model aquatic ecosystems, apparently such has not been the case

TABLE 1

Occurrence of TCBs in Water*

Compound	Location	Source	Concentration (µg/l)
1,2,3-TCB	Catawba Creek, NC	Municipal discharge	21-46^{a}
1,2,4-TCB	Catawba Creek, NC	Industrial discharge	12^{a}
	Chattanooga Creek, TN	Industrial discharge	500^{b}
	Joint Water Pollution Control Plant (JWPCP)	Municipal waste water	6.0; 1.8^{a}
	Hyperion Sewage Treatment Works, LA (HSTW)	5 mile effluent, municipal waste water	6.7; 3.1^{c}
	HSTW	7 mile effluent, municipal waste water	275; 130^{c}
	Orange County Sewage Department (OCSD)	Municipal waste water	0.30^{a}
	Port Loma Sewage Treatment Plant (PLSTP)	Municipal waste water	0.23; <0.01^{c}
	Oxnard, CA Sewage Treatment Plant (OSTP)	Municipal waste water	0.9; 0.25^{c}
	Los Angeles River	Surface run off	0.007^{d}
1,3,5-TCB	Holston River, TN	Industrial discharge	26
	JWPCP	Municipal waste water	0.2; 0.8^{c}
	HSTW	5 mile effluent, municipal waste water	<0.01; <0.01^{c}
	HSTW	7 mile effluent, municipal waste water	0.9; <0.2^{c}
	OCSD	Municipal waste water	0.2
	PLSTP	Municipal waste water	0.02; <0.01^{c}
	OSTP	Municipal waste water	0.4; <0.01^{c}
	Los Angeles River	Surface run off	0.006^{d}

*Source: U.S. EPA, 1977.

^{a}Summer; ^{b}Spring; ^{c}Summer, Fall; ^{d}Winter; ^{e}Fall with the TCBs. The accumulation of TCBs in the food chain depends upon their concentrations in aquatic organisms. Haas, et al. (1974) have found that 40 percent of the 1,2,4-TCB in wastewater was absorbed by microorganisms, and the suggestion has been made by EPA that the material concentrates in the cell wall. This type of information indicates that TCBs will persist in a water environment and are available for incorporation into fish. TCB has been detected in trout taken from Lake Superior and turbot taken from Lake Huron (U.S. EPA, 1977).

A bioconcentration factor BCF relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCF for a lipid-soluble compound in the tissues of various aquatic animals seems to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 182 was obtained for 1,2,4-trichlorobenzene using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 1,2,4-trichlorobenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 14.

There is some information on studies on biochemical oxygen demand (BOD) in waste water containing microorganisms from treatment plants. This information has been compiled previously (U.S. EPA, 1977) and is presented in Table 2. This table summarizes the 20-day BOD for 1,2,4-TCB. As can be seen, the results vary from no biodegradation to complete biodegradation of the 1,2,4-TCB.

Simmons, et al. (1976) also noted a lack of degradation of 1,2,4-TCB based on BOD determinations. However, direct chemical analysis indicated a 14 percent reduction of TCB concentrations in industrial wastewater after 24 hours, a 36 percent reduction in 72 hours and 43 percent reduction at seven days. This would indicate that the limitation in change of BOD is due primarily to incompletely oxidized metabolites.

Inhalation and Dermal

Vapor pressures for TCBs are shown in Table 3. These are relatively low compared to mono- and dichlorobenzenes. Nevertheless, TCBs have been detected in particulates from aerial fallout.

TABLE 2

Effects of 1,2,4-Trichlorobenzene on BOD*

Source of Organisms	BOD_{20} (percent of theoretical value)	References
Microorganisms from industrial waste treatment plant	78	Hintz, 1962
Microorganisms from industrial waste treatment plant	100	Alexander, 1972
Mixture of microorganisms from 4 different textile treatment plants	50	Porter and Snider, 1974
Microorganisms from "typical" treatment plant	0 (2 days)	Haas, et al. 1974

*Source: U.S. EPA, 1977.

TABLE 3

Vapor Pressures of Trichlorobenzenes*

TCB-isomer	Vapor Pressure (mm Hg)	Temperature (°C)
1,2,3	0.07	25
	1.0	40
1,2,4	0.29	25
	1.0	38.4
1,3,5	0.15	25
	1.0	78

*Source: U.S. EPA, 1977; Sax, 1975.

In a study of aerial fallout in southern California (spring, 1976), five B sampling sites showed median levels of "less than 11 ng/m^2/day" for 1,2,4-TCB and "less than 6 ng/m^2/day" for 1,3,5-TCB (U.S. EPA, 1977).

There have been no reports of exposures of humans to TCB via inhalation that resulted in toxicity. The amount of TCB necessary to induce a toxic reaction via application to the skin is quite high and thus exposure to TCB via water on the skin is not considered to be a significant factor in the determination of criteria standards (Brown, et al. 1969).

PHARMACOKINETICS

Absorption

All three isomers of TCB are absorbed from the gastrointestinal tract, intact skin, and lungs. However, the absorption is somewhat less than that seen for the monochlorinated and dichlorinated benzenes (U.S. EPA, 1977)

Metabolism

The primary route of metabolism of TCBs is via the formation of monophenols with very little, if any, formation of mercapturic acid or catechols (Williams, 1959; Parke and Williams, 1960; Kohli, et al. 1976). Kohli, et al. (1976) reported that in the rabbit, the major metabolite of 1,2,3-TCB was 2,3,4-trichlorophenol (2,3,4-TCP) (11 percent of the dose) with minor metabolites being 2,3,6-TCP (1 percent) and 3,4,5-TCP (2 percent). For 1,2,4-TCP, the monophenols were in the form of 2,4,5-TCP and 2,3,5-TCP both present in approximately the same percentage of the original dose (5 and 6 percent, respectively). In the case of

1,3,5-TCB, the two metabolites were 2,3,4-TCP and 2,4,6-TCP (1.5 and 3.0 percents, respectively). These authors proposed a pathway for metabolism which goes through arene oxide steps as shown in Figure 1. Parke and Williams (1960) have also described small quantitites of monochlorobenzene and parachlorophenol in the urine of rabbits following the administration of 1,3,5-TCB. It can be assumed that the TCB is transformed by the NADPH-cytochrome P-450 microsomal enzyme system. Although the evidence suggests this metabolic mechanism, the experiments designed to demonstrate this point specifically have not been conducted. Egyankor and Franklin (1977) incubated TCB isomers with rat hepatic microsomal cytochrome P-450. They found that the order of affinity of the isomers for cytochrome P-450 was 1,2,3-TCB <1,2,4-TCB <1,3,5-TCB. Interestingly, this is the same order which has been found for the metabolism of TCB isomers to phenol. They also noted that 1,3,5-TCB inhibits the hepatic microsomal mixed function oxidase system while 1,2,3-TCB and 1,2,4-TCB enhanced it. Ariyoshi, et al. (1975a,b,c) reported on the microsomal enzyme systems in intact rats. They found that 1,3,5-TCB increased the amount of microsomal protein, phospholipids, and cytochrome P-450 as well as stimulating the activities of aminopyrine demethylase, aniline hydroxylase, and delta aminolevulinic acid synthetase (Ariyoshi, et al. 1975a). Similar results were obtained for 1,2,4-trichlorobenzene. Increases were observed in cytochrome P-450 content of the liver, enhanced delta aminolevulinic acid synthetase activity,

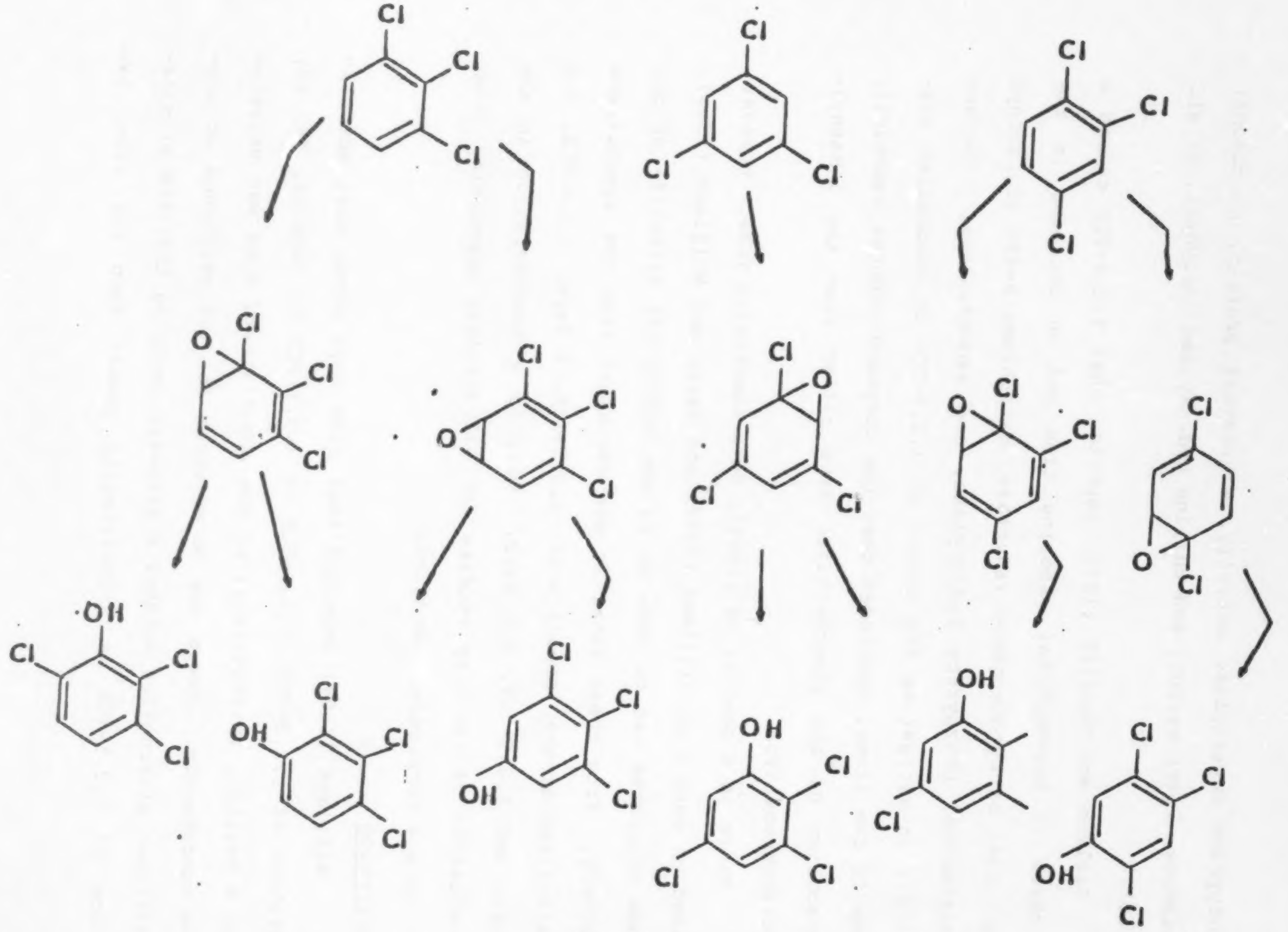
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FIGURE 1

Proposed Pathways for the Biotransformation of Trichlorobenzene Isomers Through Arene Oxide Intermediates

Source: Kohli, et al. 1976

aminopyrine demethylase activity, microsomal protein, microsomal phosphate, liver weight, and aniline hydroxylase (Ariyoshi, et al. 1975b).

Carlson and Tardiff (1976) reported that 1,2,4-TCB caused a decrease in hexobarbital sleeping time and an increase in the activities of cytochrome-c reductase, cytochrome P-450 glucuronyl transferase, benzpyrene hydroxylase, and azoreductase. Carlson (1978), investigating the effect of 1,2,4-TCB on metabolism systems in the liver, concluded that the compound induces xenobiotic metabolism of the phenobarbital type rather than the 3-methylcholanthrene type.

There is a paucity of kinetic data concerning TCBs. However, based on data from Williams (1959) and Parke and Williams (1960), some estimates can be made as to the biological half-life of the isomers. From these data, it was estimated that the approximate half-lives of the isomers are: 1,2,3-TCB, 2 days; 1,2,4-TCB, 5.5 days; and 1,3,5-TCB, 8.5 days. This is a consideration in the evaluation of toxicity studies for all species, especially those which are considered subchronic.

Excretion

Williams (1959) reported that five days after oral administration of 1,2,3-TCB, 1,2,4-TCB or 1,3,5-TCB to rabbits, 78, 42, or 9 percent, respectively, of the administered dose was excreted as monophenols. There was no evidence for the existence of significant alternative metabolic pathways implying that the elimination of 1,3,5-TCB is significantly slower than the other two isomers. This is related to the ease of oxidation of the various isomers and is reflected in the monophenol metabolites excreted.

EFFECTS

Acute, Subacute, and Chronic Toxicity

There is a limited amount of relevant data on the toxicity of 1,2,4-TCB and essentially no data on the toxicity of the other two isomers. Cameron, et al. (1937) first described hepatotoxic effects of trichlorobenzene, finding it to be less than that of monochlorobenzene or orthodichlorobenzene. Brown, et al. (1969) reported the single dose acute oral LD_{50} in rats to be 756 mg/kg (556 to 939 mg/kg, 95 percent confidence limits). In mice, the single dose acute oral LD_{50} was 766 mg/kg (601 to 979 mg/kg, 95 percent confidence limits). With the rats, deaths occurred within five days of exposure and in mice within three days of exposure. For both species, intoxication was manifested as depression of activity at low doses and predeath extensor convulsions at lethal doses. They also determined a single dose acute percutaneous toxicity in rats. This was 6139 mg/kg (4299 to 9056 mg/kg, 95 percent confidence limits). From the same study, data on skin irritation were reported. The authors concluded that 1,2,4-TCB was not very irritating, although fissuring typical of a defatting action was observed after prolonged contact in rabbits and guinea pigs. Spongiosis, acanthosis, and parakeratosis were noted in both species along with some inflammation of the superficial dermis in rabbits exposed daily for three weeks. Some guinea pigs exposed to 0.5 ml/day for 5 days/week for three weeks died following extensor convulsions. The livers of these animals were found to have necrotic lesions.

Coate, et al. (1977) reported on a chronic inhalation exposure of rats (30 animals per group), rabbits (16 animals per group) and monkeys (9 animals per group) to 1,2,4-TCB at 25, 50, and 100 ppm for periods of up to 26 weeks. No exposure-related ophthalmologic changes were detected in rabbits and monkeys after 26 weeks of exposure (rats were not examined). Similarly, no exposure-related changes were detected in BUN, total bilirubin, SGOT, SGPT, alkaline phosphatase and LDH when determined at 4, 13, and 26 weeks of exposure. Hematological values were also normal when examined at 4, 13, and 26 weeks. Pulmonary function tests were conducted on the monkeys. No treatment-associated changes were noted in static compliance, carbon monoxide diffusion capacity, distribution of ventilation, transpulmonary pressure, or a battery of lung volume determinations. Histological changes were noted in the livers and kidneys of rats necropsied after 4 and 13 weeks of exposure. These changes were noted in animals from all treatment groups and were manifested as an increase in size and vacuolation of hepatocytes. However, after 26 weeks, no compound-related histopathological changes were noted in rabbits or monkeys.

Rowe (1975) reported that persons exposed to 1,2,4-TCB vapor at 3 to 5 ppm experienced minor eye and respiratory irritation.

The odor was described as easily noticeable at these concentrations. There was a detectable odor at concentrations up to 2.4 ppm, but no eye irritation was evident. No odor was noted at concentrations up to 0.88 ppm.

Smith, et al. (1978) conducted a 90-day, daily oral dose study of 1,2,4-TCB in rhesus monkeys (four animals per group) at concentrations of 1, 5, 25, 90, 125, and 174 mg/kg. Their report, which is an abstract, states that single oral daily doses of 25 mg/kg or less were nontoxic whereas doses of 90 mg/kg or higher were toxic and doses of 173.6 mg/kg were lethal within 20 to 30 days. There were no deaths observed in the 1, 5, and 25 mg/kg groups; one death occurred in each of the 90 mg/kg and 125 mg/kg groups and two deaths occurred in the 174 mg/kg group. Animals on the highest dose exhibited severe weight loss and predeath fine tremors. All of the animals in the highest dose group had elevated BUN, Na^+, K^+, CPK, SGOT, SGPT, LDH, and alkaline phosphatase as well as hypercalcemia and hyperphosphatemia from 30 days on. Smith, et al. (1978) have been using the urinary pattern of chlorguanide metabolites as an indication of cytochrome P-450 dependent drug metabolism. The abstract states that at the high doses, monkeys showed evidence of the hepatic induction as well as increased clearance of intravenous doses of labeled TCB. Further information on the study (Smith, personal communication) gave evidence of liver enzyme induction in the 90, 125, and 174 mg/kg animals. There were some pathological changes noted in the livers of the high dose groups, primarily a fatty infiltration. The point at which there was no effect related to the compound was at the 5 mg/kg level. Since only an abstract of this study is available and since the interpretation of this study is complicated by the use of other drugs and weight losses in the control animals, a valid no-observed-effect level (NOEL) cannot be derived from these data.

Rimington and Ziegler (1963) were able to induce an experimental porphyria in rats with 1,2,4-TCB which was marked by an increased urinary coproporphyrin excretion and an increased porphorobilinogen excretion in urine. This porphyria could be reversed by glutathione. They also noted a hair loss due to hyperkeratosis. This study cannot be used for criterion formulation because the compound was given only at one (maximum tolerated) dose.

Synergism and/or Antagonism

In general, the halogenated benzenes appear to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides, and other xenobiotics. Exposure to TCB could, therefore, result in decreased pharmacologic and/or toxicologic activity of numerous compounds. Frequently, chemical agents are metabolized to more active or toxic "reactive" intermediates. In this event, exposure to TCB would result in enhanced activity and/or toxicity of these agents.

Teratogenicity, Mutagenicity and Carcinogenicity

Studies have not been conducted primarily for the purpose of determining the teratogenic or mutagenic properties of trichlorobenzene isomers. Gotto, et al. (1972), in a study to examine hepatomas caused by hexachlorocyclohexane, administered 1,2,4-TCB at a dose of 600 ppm by inhalation daily for six months to mice and reported no incidence of hepatomas. There are no other studies which have been designed for the purpose of studying carcinogenicity of TCB; nor have there been any other reports indicating such activity.

CRITERION FORMULATION

Existing Guideline and Standards

A proposed American Conference of Governmental and Industrial Hygienists Threshold Limit Value (TLV) for 1,2,4-trichlorobenzene is 5 ppm (40 mg/m^3) as a ceiling value (ACGIH, 1979). Sax, et al. (1975) recommends a maximum allowable concentration of 50 ppm in air for commercial TCB, a mixture of isomers. Coate, et al. (1977), citing their studies, recommended that the TLV should be set below 25 ppm, preferably at 5 ppm (40 mg/m^3). Gurfein and Parlova (1962) indicate that in the Soviet Union the maximum allowable concentration for TCB in water is 30 µg/l, which is intended to prevent organoleptic effects. They also report that in a study of 40 rats and 8 rabbits administered TCB in drinking water at 60 µg/l for 7 to 8 months, no effects were observed. This information was obtained from an abstract only, as evaluation of the study was not possible.

Current Levels of Exposure

Possible human exposure to TCBs might occur from municipal and industrial wastewater and from surface runoff (U.S. EPA, 1977). Municipal and industrial discharges contained from 0.1 µg/l to 500 µg/l. Surface runoff has been found to contain 0.006 to 0.007 µg/l.

In the National Organics Reconaissance Survey (NORS) conducted by EPA in 1975, trichlorobenzene was found in drinking water at a level of 1.0 µg/l.

Basis and Derivation of Criterion

Reliable toxicologic data on which to base a defensible water quality criterion do not exist for the trichlorobenzenes. The studies by Smith, et al. (1978) and Coate, et al. (1977) do not give sufficient detail or suffer from inherent problems in experimental design. Therefore, according to the guidelines for criterion development, a criterion cannot be recommended for any trichlorobenzene isomer. For future derivation of a human health criterion, sound data must be developed describing the effects of trichlorobenzenes on humans and experimental animals.

REFERENCES

Alexander, M. 1972. Pollution characteristics of 1,2,4-trichlorobenzene. Dow Chemical Co., Midland, Michigan. (Unpub.)

American Conference of Governmental Industrial Hygienists. 1979. Threshold Limit Values for Chemical Substances and Physical Agents in Workroom Environment with Intended Changes for 1979.

Ariyoshi, T., et al. 1975a. Relation between chemical structure and activity. I. Effects of the number of chlorine atoms in chlorinated benzenes on the components of drug metabolizing systems and hepatic constitutents. Chem. Pharm. Bull. 23: 817.

Ariyoshi, T., et al. 1975b. Relation between chemical structure and activity. II. Influences of isomers of dichlorobenzene, trichlorobenzene and tetrchlorobenzene on the activities of drug metabolizing enzymes. Chem. Pharm. Bull. 23: 824.

Ariyoshi, T., et al. 1975c. Relation between chemical structure and activity. III. Dose response on tissue course of induction of microsomal enzymes following treatment with 1,2,4-trichlorobenzene. Chem. Pharm. Bull. 23: 831.

Brown, V.K.H., et al. 1969. Acute toxicity and skin irritant properties of 1,2,4-trichlorobenzene. Ann. Occup. Hyg. 12: 209.

Cameron, G.R., et al. 1937. The toxicity of certain chlorine derivatives of benzene with special reference to o-dichlorobenzene. Jour. Path. Bact. 44: 281.

Carlson, G.P. 1978. Induction of cytochrome P-450 by halogenated benzenes. Biochem. Pharmacol. 27: 361.

Carlson, G.P. and R.G. Tardiff. 1976. Effect of chlorinated benzenes on the metabolism of foreign organic compounds. Toxicol. Appl. Pharmacol. 36: 383.

Coate, W.B., et al. 1977. Chronic inhalation exposure of rats, rabbits and monkeys to 1,2,4-trichlorobenzene. Arch. Environ. Health 32: 249.

Egyankor, K.B. and C.S. Franklin. 1977. Interaction of the trichlorobenzenes with cytochrome P-450. Biochem. Soc. Trans. 5: 1519.

Gotto, M., et al. 1972. Hepatoma formation in mice after administration of high doses of hexachlorocyclohexane isomers. Chemosphere. 1: 279.

Gurfein, L.W. and Z.K. Parlova. 1962. The Limit of Allowable Concentration of Chlorobenzenes in Water Basins. In: B.S. Levine (ed.), USSR Literature on Water Pollution. Dept. Commer., Washington, D.C.

Haas, J.M., et al. 1974. Environmental considerations concerning the selection of dye carrier solvents. Presented at the 1974 Am. Assoc. Textile Chem. Colourists Natl. Tech. Conf. October 9-11.

Hintz, M. 1962. Pollution characteristics of 1,2,4-trichlorobenzene. Dow Chemical Co., Midland, Michigan. (Unpub.)

Johnson, K. 1980. Memorandum to D.W. Kuehl. U.S. EPA. March 10.

Kohli, I., et al. 1976. The metabolism of higher chlorinated benzene isomers. Can. Jour. Biochem. 54: 203.

Kujawa, M., et al. 1977. On the Metabolism of Lindane. Proc. 1st Int. Symp. Environ. Pollut. Human Health.

Parke, D.V. and R.T. Williams. 1960. Studies in detoxication. Metabolism of halobenzenes: (a) Penta- and hexachlorobenzene: (b) Further observations on 1,3,5-trichlorobenzene. Biochem. Jour. 74: 1.

Porter, E.M. and J.J. Snider. 1974. 30-day biodegradability of textile chemicals and dyes. Presented at 1974 Am. Assoc. Textile Chem. Colourists Natl. Tech. Conf. October 9-11.

Rimington, C. and G. Ziegler. 1963. Experimental porphyria in rats induced by chlorinated benzenes. Biochem. Pharmacol. 12: 1387.

Rowe. 1975. Written communication. April.

Sax, N.I. 1975. Dangerous Properties of Industrial Materials. 4th ed. Van Nostrand Reinhold, New York.

Simmons, P., et al. 1976. 1,2,4-Trichlorobenzene: Biodegradable or not? Can. Assoc. Textile Colourists Chem. Int. Tech. Conf. Quebec. October 13-15.

Smith, C.C. 1979. Personal communication. April 10.

Smith, C.C., et al. 1978. Subacute toxicity of 1,2,4-trichlorobenzene (TCB) in subhuman primates. Fed. Proc. 37: 248.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Rep. Cong. No. PB-250961.

U.S. EPA. 1977. Investigation of selected potential environmental contaminants: Halogenated benzenes. EPA 560/2-77-004.

U.S. EPA. 1978. In depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency. Contract No. 68-01-4646.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, Calif. Final rep. Task II, Contract No. 68-01-3887.

U.S. International Trade Commission. 1975. Synthetic organic chemicals: U.S. production and sales. U.S. Govt. Print. Off., Washington, D.C.

Williams, R.T. 1959. The Metabolism of Halogenated Aromatic Hydrocarbons. In: Detoxication Mechanisms. 2nd ed. John Wiley and Sons, New York. p. 237.

TETRACHLOROBENZENE

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Tetrachlorobenzene (TeCB) exists as three isomers-1,2,3,4-TeCB, 1,2,3,5-TeCB and 1,2,4,5-TeCB. Of these, 1,2,4,5-TeCB is the most widely used. 1,2,4,5-TeCB is used primarily in the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenol (2,4,5-TCP). In 1973, an estimated ten million pounds of 1,2,4,5-TeCB were utilized in the manufacture of 2,4,5-T while six million pounds were utilized in the manufacture of 2,4,5-TCP (U.S. EPA, 1977). In the Soviet Union, 1,2,4,5-TeCB is used as a soil and grain pesticide (Fomenko, 1965). It is not used for this purpose in the United States.

Tetrachlorobenzene (TeCB) has been found to be among the metabolites of hexachlorobenzene (Mehendale, et al. 1975; Rozman, et al. 1975), lindane, pentachlorocyclohexane, pentachlorobenzene, and pentachlorophenol (Engst, et al. 1976a,b).

1,2,4,5-TeCB has an extremely low vapor pressure, less than 0.1 mm Hg at 25°C (Sax, 1975). The log of the octanol/water partition coefficient for TeCB is 4.93.

EXPOSURE

Ingestion from Water

No literature was found which identified TeCB in water in the United States. However, contamination of runoff as a result of its industrial use is certainly feasible and may in part, be responsible for the contamination of the aquatic organisms described below. Soil microorganisms are capable of metabolizing lindane to tetrachlorobenzene, among others (Tu, 1976; Mathur and Saha, 1977). TeCB derived in this manner is available from soil runoff.

Ingestion from Food

There are some data to show that TeCB will concentrate in fish exposed to industrial effluent discharge. Kaiser (1977) identified two isomers of TeCB in three species of fish caught at various distances from a pulp and paper mill. Similarly, Lunde and Ofstad (1976) identified tetrachlorobenzene in sprat (a small herring) from different locations in southeastern Norway.

Qualitatively, tetrachlorobenzenes have been identified in the food chain as a result of the biotransformation of lindane. Saha and Burrage (1976) administered lindane to hen pheasants and identified tetrachlorobenzene as part of the array of metabolites found in eggs and chicks as well as in the body tissues of the hens. Balba and Saha (1974) followed the metabolism of ^{14}C-lindane in wheat plants grown from treated seeds and identified two and possibly three of the isomers of TeCB. Kohli, et al. (1976 b,c) in laboratory studies identified TeCB as a minor metabolite of lindane in lettuce and endives.

Tetrachlorobenzenes have also been identified as metabolites of gamma pentachlorocyclohexane in corn and pea seedlings. Pentachlorobenzenes have also been identified in the essential oil of marsh grass (Miles, et al. 1973).

There is legitimate doubt as to whether exposure to TeCBs as breakdown products of lindane and other substances represents a significant exposure, especially considering that concentrations of the more toxic parent compounds are higher.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 1,800 was obtained for 1,2,3,5-tetrachlorobenzene using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 1,2,3,5-tetrachlorobenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 1,125.

No measured steady-state bioconcentration factor is available for 1,2,4,5-tetrachlorobenzene. However, the weighted average BCF of 1,125 obtained for the very similar 1,2,3,5-tetrachlorobenzene can also be used for this compound.

Inhalation and Dermal

No reliable information has been located dealing with inhalation or dermal exposure to TeCB.

PHARMACOKINETICS

Absorption, Distribution, Metabolism, Excretion

Jondorf, et al. (1958) administered each of the three isomers of TeCB to three rabbits at oral doses of 0.5 g/kg. The animals were followed for six days after dosing. The percentage of administered dose recovered in the feces over this time for the respective compounds was: 1,2,3,4-TeCB, 5 percent; 1,2,3,5-TeCB, 14 percent; and 1,2,4,5-TeCB, 16 percent. Considering that this is over a six-day period and that some of the fecal TeCB content could possibly have been a result of biliary excretion, it would appear that the gastrointestinal absorption of TeCBs is relatively efficient.

Table 1 shows the distribution of unchanged TeCB in rabbit tissues six days after dosing. Comparative distribution among the three isomers shows a relative degree of consistency. The one exception is in the gut contents where 12 percent of the total remaining compound is present for 1,2, 4,5-TeCB which is about twice

TABLE 1

Unchanged Tetrachlorobenzene in Rabbit Tissues,
Six Days After Dosing (0.5 g/kg orally)*

	Percentage of Dose						
TeCB	Liver	Brain	Skin	Depot Fat	Gut Contents	Rest of Body	Total
1,2,3,4	0.1	-	2	5	0.5	2.0	10
1,2,3,5	<0.5	<0.2	5	11	1.4	5.2	23
1,2,4,5	0.1	<0.1	10	25	6.2	6.4	48

*Source: Jondorf, et al. 1958.

that for the other isomers. This could reflect lesser absorption of 1,2,4,5-TeCB or, possibly, biliary excretion.

Table 2 shows the extent of elimination of the isomers in expired air.

Table 3 shows the urinary excretory pattern observed in the three isomers. The 1,2,3,4-TeCB isomer is more freely metabolized than the other two isomers, and 1,2,4,5-TeCB is metabolized the least.

Kohli, et al. (1976a) studied the metabolism of TeCB isomers in rabbits and identified the nature of TCP metabolites. A dose of 60 to 705 mg/kg was administered to rabbits by intraperitoneal injection and the urine and feces were collected for ten days. The metabolism of both 1,2,3,4-TeCB and 1,2,3,5-TeCB yielded two common metabolites, 2,3,4,5- and 2,3,4,6-tetrachlorophenol (TeCP). Another metabolite of 1,2,3,5-TeCB was 2,3,5,6-TeCP. This metabolite 2,3,5,6-TeCP was also the only metabolite identified following the administration of 1,2,4,5-TeCB. The relationships among the various isomers were strikingly similar to the data reported by Jondorf, et al. (1958).

Kohli, et al. (1976a) proposed the formation of the phenol metabolites through corresponding arene oxides. The authors suggested the involvement of an " NIH shift" of the chlorine atom in the formation of the metabolites (except for the formation of 2,3,5,6-TeCP from 1,2,3,5-TeCB which can be derived from 2,3,5,6-TeCB and oxide without an NIH shift of chlorine). The scheme proposed by Kohli is shown in Figure 1.

TABLE 2

Elimination of Unchanged Tetrachlorobenzenes in Expired Air of Rabbits Following Oral Dosing*

TeCB	Dose (g/kg)	Percentage of Dose in Expired Air Days after Dosing					Total
		1	2	3	4	5	
1,2,3,4	0.5	1.9	2.2	1.6	0.2	-	5.9
	0.3	0.8	1.7	6.7	-	-	9.2
1,2,3,5	0.5	2.1	2.1	1.2	2.9	2.6	10.9
	0.3	0.9	3.2	9.8	-	-	13.9
1,2,4,5	0.5	1.2	0.2	0.2	-	-	1.6

*Source: Jondorf, et. al. 1958.

TABLE 3

Urinary Excretion of Metabolites of Tetrachlorobenzenes in Rabbits Following Oral Dosing (0.5 g/kg/)*

	Percentage of Dose Excreted				
TeCB	Glucuronide	Ethereal Sulfates	Mercapturic Acid	TeCP Feces	Total
1,2,3,4	30(22-36) (5)	3(1-8)	<1	8(7,9)	43(38,48) (2)
1,2,3,4	6(2-10) (9)	2(1-6) (9)	0 (3)	1.9(1.2,2.5) (2)	5(4.6) (2)
1,2,4,5	4(1-8) (11)	1(<1-2) (11)	0 (3)	1.3(0.9,1.6) (2)	2.2(0.9,1.6) (2)

*Source: Jondorf, et al. 1958.

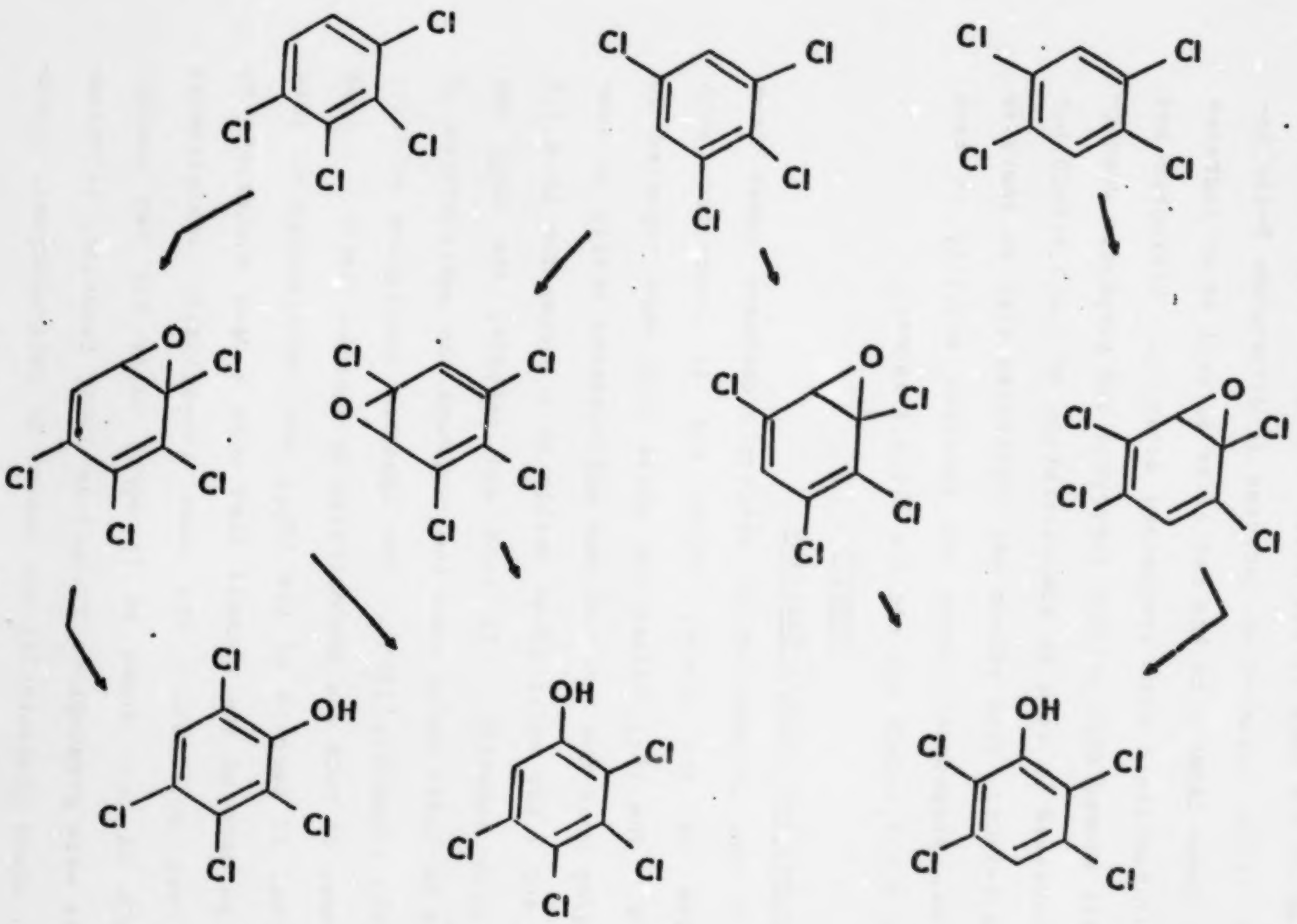

FIGURE 1

Proposed Routes for the Biotransformation of Tetrachlorobenzene
Isomers Via Arene Oxides
Source: Kohli, et al. 1976a

From the above information, it is reasonable to expect that the metabolism of the TeCB is via liver microsomal enzymes. Ariyoshi, et al. (1975) reported an increase in cytochrome P-450 induced by all three isomers in the rat liver as well as an increase in delta aminolevulinic acid synthetase activity. Rimington and Ziegler (1963) showed that urinary porphyria and porphyria precursors were increased in rats by administration of 1,2,3,4-TeCB but not by 1,2,4,5-TeCB. This effect was correlated with an increase in porphyrins, porphorobilinogen and catalase activity in rats treated with 1,2,3,4-TeCB but not the 1,2,4,5 isomer.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Most of the information on tetrachlorobenzene comes from studies done in the Soviet Union and is concerned with 1,2,4,5-TeCB. The LD_{50} values for white mice were reported to be 1,035 mg/kg when the compound was administered orally in sunflower oil and 2,650 mg/kg given orally as a suspension in a 1.5 percent starch solution. In rats and rabbits, the LD_{50} was reported to be 1,500 mg/kg when the compound was administered in sunflower oil (Fomenko, 1965). The apparent cumulative activity of this isomer of TeCB was demonstrated by Fomenko (1965). A dose of 300 mg/kg, 20 percent of the LD_{50}, was administered to rats daily; 50 percent of the animals died when a dose equivalent to the LD_{50} was obtained. The same investigator administered 1,2,3,5-TeCB in oral doses of 75 mg/kg daily for two months. While there were presumptive changes in liver function, prothrombin index, blood cholesterol, and number of reticulocytes, histopathological examination showed no significant change that would alter liver function. Adrenal hypertrophy and decreased content of ascorbic acid in adrenals were reported. Histopathological examinations did not reveal appreciable differences between control and experimental groups.

Further experiments are described in the foregoing report (Fomenko, 1965) from the Soviet Union in which 1,2,4,5-TeCB was administered in oral doses of 0.001, 0.005, and 0.05 mg/kg to rats and rabbits over an 8-month period. The report states that doses of 0.005 mg/kg and "especially" 0.05 mg/kg disrupted the conditioned reflexes. It is stated that "formation of a positive conditioned reflex became slower but the latent period remained the same." It is also stated that rabbits treated with doses of 0.05 mg/kg "began to display disorders in glycogen-forming function in the liver only after six experimental months." No hematologic changes were noted in the animals. At the end of the dosing period, liver weights were increased in animals receiving doses of 0.005 and 0.05 mg/kg. The conclusion was that the two higher doses were active and that the lower dose was not.

The data from the above studies (Fomenko, 1965) are only partially presented and the bulk of the report consists of the conclusions of the author. The studies of conditioned reflexes in rats were conducted on a control group of five animals, low and middle dose groups of seven animals each, and a high dose group of six animals. It is not clear from the report whether these animals represented the total number of animals in each group.

Braun, et al. (1978) administered 1,2,4,5-TeCB in the diet to beagles at 5 mg/kg/day for two years. No changes in clinical chemistry parameters were noted after 18 months. At 24 months there was a slight elevation of serum alkaline phosphatase activity and bilirubin levels. The animals were then allowed to recover. After three months the serum chemistry changes noted were no longer evident. Gross and histopathological studies were done 20 months after cessation of exposure. No treatment related changes were noted.

Synergism and/or Antagonism

Since TeCBs can increase cytochrome P-450 levels, it, like other halogenated benzenes, appears to induce metabolic enzymes (Ariyoshi, et al. 1975). In general, the halogenated benzenes appear to increase the activity of microsomal NADPH-cytochrome P-450-dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides, and other xenobiotics. Exposure to TeCB could, therefore, result in decreased pharmacologic and/or toxicologic activity of numerous compounds. Frequently, chemical agents are metabolized to more active or toxic "reactive" intermediates. In this event, exposure to TeCB would result in enhanced activity and/or toxicity of these agents.

Teratogenicity, Mutagenicity, and Carcinogenicity

No studies have been identified which directly or indirectly address the teratogenicity or carcinogenicity of TeCB. An abstract of a study by Kiraly, et al. (1976) describes a study of chromatid disorders among workers involved in the manufacture of an organophosphorus compound. Disorders were said to be significantly higher in this group than in a group involved in the manufacture of TeCB. However, the abstract concludes, "The mutagenic properties of tetrachlorobenzene were confirmed." This is the only reference seen referring to mutagenic activity of TeCBs.

CRITERION FORMULATION

Existing Guidelines and Standards

The maximal permissible concentration of TeCB in water established by the Soviet Union is 0.02 mg/l (U.S. EPA, 1977).

Current Levels of Exposure

No data are available on current levels of exposure. However, the report by Morita, et al. (1975) gives some indication of exposure. Morita, et al. (1975) examined adipose tissue samples obtained at general hospitals and medical examiners offices in central Tokyo. Samples from 15 individuals were examined; this represented 5 males and 10 females between the ages of 13 and 78. The tissues were examined for 1,2,4,5-TeCB as well as for 1,4-dichlorobenzene and hexachlorobenzene. The TeCB content of the fat ranged from 0.006 to 0.039 mg/kg of tissue; the mean was 0.019 mg/kg. The mean concentrations of 1,4-dichlorobenzene and hexachlorobenzene were 1.7 mg/kg and 0.21 mg/kg, respectively. Neither age nor sex correlated with the level of any of the chlorinated hydrocarbons in adipose tissue.

Special Groups at Risk

The primary groups at risk from the exposure to TeCB are those who deal with it in the workplace. Since it is a metabolite of certain insecticides, it might be expected that certain individuals exposed to those agents might experience more exposure to TeCB, especially since its elimination rate might be relatively slow in man. Individuals consuming large quantities of fish may also be at risk due to the proven bioconcentration of TeCB in fish. The bioconcentration factor for 1,2,4,5-TeCB is 1,125.

Basis and Derivation of Criterion

The dose of 5 mg/kg/day 1,2,4,5-TeCB reported by Braun, et al. (1978) for beagles caused no changes in clinical chemistry parameters after 18 months of exposure via the diet. After 24 months, however, slight elevations were noted in serum alkaline phosphatase activities and bilirubin levels. These changes were reversible three months after the last exposure. Whether histopathological changes related to treatment with 1,2,4,5-TeCB occurred is unclear, as tissue studies were not begun until 20 months after cessation of exposure. Because no effects were observed at the dose level used by Braun, et al. (1978) until after 18 months of exposure, and since those changes were transient and not clearly related to any functional impairment or pathological lesions which would adversly affect the performance of the animal, 5 mg/kg/day can be considered a no-observed-adverse-effect level (NOAEL) for calculation of an acceptable daily intake (ADI). Based on a 70 kg man, the ADI can be calculated from the NOAEL using a safety factor of 1,000. This safety factor is required by the guidelines for criteria derivation because: (1) the study by Braun, et al. (1978) was performed on only four animals, (2) gross and histopathology were not done until 20 months after the last exposure; and (3) supportive epidemiologic or subchronic data are not available. For 1,2,4,5-TeCB, the ADI can be calculated as follows:

$$\text{ADI} = \frac{70 \text{ kg} \times 5 \text{ mg/kg}}{1{,}000} = 0.35 \text{ mg/day}$$

For the purpose of establishing a water quality criterion, it is assumed that on the average, a person ingests 2 liters of water and 6.5 grams of fish daily. Since fish may bioconcentrate this compound, a bioconcentration factor (F) is used in the calculation.

The equation for calculating an acceptable amount of TeCB in water is:

$$\text{Criterion} = \frac{350\ \mu g/day}{2\ l + (1{,}125 \times 0.0065)} = 37.6\ \mu g/l \text{ or } 38\ \mu g/l$$

where:

2 l = 2 liters of drinking water consumed

0.0065 kg = amount of fish consumed daily

1,125 = bioconcentration factor

ADI = Acceptable Daily Intake (mg/kg) for a 70 kg/person)

Thus, the recommended criterion for 1,2,4,5-TeCB in water is 38 µg/l. Due to the lack of data describing toxicologic effects of the other TeCB isomers and the predominant use of 1,2,4,5-TeCB by industry, no criteria are recommended for the 1,2,3,4- or 1,2,3,5-TeCB isomers. This criterion for 1,2,4,5-tetrachlorobenzene can alternately be expressed as 48 µg/l if exposure is assumed to be from the consumption of fish and shellfish alone.

REFERENCES

Ariyoshi, T., et al. 1975. Relation between chemical structure and activity. II. Influences of isomers in dichlorobenzene, trichlorobenzene and tetrachlorobenzene on the activities of drug-metabolizing enzymes. Chem. Pharm. Bull. 23: 824.

Balba, M.H. and J.G. Saha. 1974. Metabolism of lindane ^{14}C by wheat plants grown from treated seeds. Environ. Let. 7: 181.

Braun, W.H., et al. 1978. Pharmacokinetics and toxicological evaluation of dogs fed 1,2,4,5-tetrachlorobenzene in the diet for two years. Jour. Environ. Pathol. Toxicol. 2: 225.

Engst, R., et al. 1976a. The metabolism of hexachlorobenzene (HCB) in rats. Bull. Environ. Contam. Toxicol. 16: 248.

Engst, R., et al. 1976b. The metabolism of lindane and its metabolites gamma-2,3,4,5,6-pentachlorocyclohexene, pentachlorobenzene and pentachlorophenol in rats and the pathways of lindane metabolism. Jour. Environ. Sci. Health Bull: 95.

Fomenko, V.N. 1965. Determination of the maximum permissible concentration of tetrachlorobenzene in water basins. Gig. Sanit. 30: 8.

Johnson, K. 1980. Memorandum to D.W. Kuehl. U.S. EPA. March 10.

Jondorf, W.R., et al. 1958. Studies in detoxication. The metabolism of halogenobenzenes 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzenes. Jour. Biol. Chem. 69: 189.

Kaiser, K.L.E. 1977. Organic contaminant residues in fishes from Nipigon Bay Lake Superior. Jour. Fish. Res. Board Can. 34: 850.

Kiraly, J., et al. 1976. Chromosome studies in workers exposed to organophosphorus insecticides. Mankavedelem. 22: 27.

Kohli, J., et al. 1976a. The metabolism of higher chlorinated benzene isomers. Can. Jour. Biochem. 54: 203.

Kohli, J., et al. 1976b. Balance of conversion of [^{14}C] lindane in lettuce in hydroponic culture. Pestic. Biochem. Physiol. 6: 91.

Kohli, J., et al. 1976c. Contributions to ecological chemistry. CVII. Fate of ^{14}C-lindane in lettuce, endives and soil under outdoor conditions. Jour. Environ. Sci. Health B11: 23.

Lunde, G. and E.B. Ofstad. 1976. Determination of fat soluble chlorinated compounds in fish. Jour. Anal. Chem. 282: 395.

Mathur, S.P. and J.G. Saha. 1977. Degradation of lindane-^{14}C in a mineral soil and in an organic soil. Bull. Environ. Contam. Toxicol. 17: 424.

Mehendale, H.M., et al. 1975. Metabolism and effect of hexachlorobenzene on hepatic microsomal enzymes in the rat. Jour. Agric. Food Chem. 23: 261.

Miles, D.H., et al. 1973. Constituents of marsh grass. Survey of the essential oils in Juncus roemerians. Phytochemistry 12: 1399.

Morita, M., et al. 1975. A systematic determination of chlorinated benzenes in human adipose tissue. Environ. Pollut. 9: 175.

Rimington, C. and G. Ziegler. 1963. Experimental porphyria in rats induced by chlorinated benzenes. Biochem. Pharmacol. 12: 1387.

Rozman, K., et al. 1975. Separation, body distribution and metabolism of hexachlorobenzene after oral administration to rats and rhesus monkeys. Chemosphere. 4: 289.

Saha, J.G. and R.H. Burrage. 1976. Residues of lindane and its metabolites in eggs, chicks and body tissues of hen pheasants after ingestion of lindane carbon-^{14} via treated wheat seed or gelatin capsules. Jour. Environ. Sci. Health Bll: 67.

Sax, N.I. 1975. Dangerous properties of industrial materials. 4th ed. Van Nostrand Reinhold, New York. p. 1145.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Tu, C.M. 1976. Utilization and degradation of lindane by soil microorganisms. Arch. Microbiol. 108: 259.

U.S. EPA. 1977. Investigation of selected potential environmental contaminants: halogenated benzenes. 560/2-77-004. U.S. Environ. Prot. Agency.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency. Contract NO. 68-01-4646.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, Calif. Final rep., Task II, Contract No. 68-01-3887.

PENTACHLOROBENZENE

Mammalian Toxicology and Human Health Effects

INTRODUCTION

Pentachlorobenzene (QCB*) is used primarily as a precursor in the synthesis of the fungicide, pentachloronitrobenzene (PCNB, Quintozene, Terraclor), and as a flame retardant. It has been suggested as an intermediate in the production of thermoplastics (Kwiatkowski, et al. 1976). QCB is a white solid crystalline material at room temperature and, like other halogenated benzenes, is both lipophilic and hydrophobic. Approximately 1.4 x 10^6 kg of pentachlorobenzene was produced in 1972 and it is estimated that 16.6 x 10^3 kg of the material was discharged into ambient water sources. Much of the exposure of the population to QCB is derived from exposure to lindane, hexachlorobenzene (HCB), and PCNB. The metabolism of lindane to QCB is well established, and it has been demonstrated in humans (Engst, et al. 1976a), rats (Engst, et al. 1976b,c; Seidler, et al. 1975; Kujawa, et al. 1977), and rabbits (Karapally, et al. 1973). Biotransformation of lindane to QCB can occur earlier in the food chain. Engst, et al. (1977) identified QCB as a product of the metabolism of lindane by mold grown spontaneously on grated carrots. Tu (1976) identified

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*QCB (for quintochlorobenzene) rather than PCB will be used as the abbreviation for pentachlorobenzene to avoid confusion with polychlorinated biphenyls.

71 soil microorganisms which would biodegrade lindane. Thirteen of these were examined further and were found to produce QCB as one of the metabolites of the insecticide. Mathur and Saha (1977) have also reported QCB as a soil degradation product of lindane.

QCB has been identified as a metabolite of HCB in rats (Mehendale, et al. 1975; Engst, et al. 1976c) and rhesus monkeys (Rozman, et al. 1977, 1978; Yang, et al. 1975, 1978).

Tetrachloronitrobenzene (TCNB) occurs as a residue in technical grade PCNB. Borzelleca, et al. (1971) detected TCNB storage in tissue of rats, dogs, and cows following feeding studies with PCNB. Rautapaa, et al. (1977) examined soil samples in Finland from areas that have been treated with PCNB and found a maximum PCNB level of 27 mg/kg of soil and the highest QCB level of 0.09 mg/kg of soil.

Igarashi, et al. (1975) identified QCB as a further degradation product of pentachlorothioanisole in soil.

The importance of QCB as a contaminant of PCNB in treated soil is demonstrated by the study of Beck and Hansen (1974). They studied 22 soil samples from fields where technical PCNB had been used regularly during the foregoing 11 years. The concentration range for PCNB in the samples was from 0.01 to 25.25 mg/kg of soil and for QCB was from 0.003 to 0.84 mg/kg of soil. The samples were studied for a period of 600 days. The half-life of QCB in two separate determinations was 194 and 345 days. The calculated log octanol/water partition coefficient for QCB = 5.63.

EXPOSURE

Ingestion from Water

The following discussion concerning the ingestion of QCB from food, especially as related to its presence in marine organisms, also relates to the presence of the compound in water. Burlingame (1977) has identified QCB in effluent from a wastewater treatment plant in southern California. Access to water by QBC can occur by a number of means including industrial discharge or as a breakdown product or contaminant of widely used organochlorine compounds.

Ingestion from Food

From the available information, it appears that the presence of QCB in soil and its persistence there can result in accumulation within the food chain. This also holds true for its ecological precursors. For example, Balba and Saha (1974) treated wheat seed with isotopically labeled lindane and observed a number of metabolites, including QCB, in the seedlings and mature plants. Kohli, et al. (1976a) found that isotopically labeled lindane added to the nutrient medium for lettuce was metabolized to a number of products including QCB. Dejonckheere, et al. (1975, 1976) examined samples from soil which had been used to grow lettuce and witloof-chicory. The soil had been treated with PCNB for a 6-year period. Average QCB concentrations ranged from 0.25 to 0.85 ppm. Lunde (1976) has examined fish from southeastern Norway for the presence of polychlorinated aromatic hydrocarbons. QCB was among a number of compounds identified in extracts of plaice, eel, sprat, whiting, and cod. Lunde and Ofstad (1976) quantitated the amount of chlorinated hydrocarbons in sprat oil. Six samples taken from different locations and/or at different times contained QCB at 0.7 to 3.8 ppm. Ten Berge and Hillebrand (1974) identified the presence of a number of organochlorine compounds, including QCB, in plankton, shrimp, mussels, and fish from the North Sea and the Dutch Wadden Sea. The compounds were present at part per billion levels.

Stijve (1971) detected QCB in chicken fat which was ascribed to residues of HCB. Kazama, et al. (1972) administered QCB by intramuscular injection to hens and recovered 7.3 percent of the dose in the yolk of the egg. No material was found in the egg white. Saha and Burrage (1976) administered isotopically labeled lindane to hen pheasants via treated wheat seed or gelatin capsules and recovered QCB as one of the metabolites in the body of the hen, in the eggs and in the chicks. Dejonckheere, et al. (1974) reported on the presence of QCB in animal fat and suggested that it was derived from pesticide residues of HCB and lindane in feed. Greve (1973) identified QCB and HCB in wheat products used for animal feed and detected QCB in the fat of animals utilizing that feed.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCF for a lipid-soluble compound in the tissues of various aquatic animals seems to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stepahn, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 3,400 was obtained for pentachlorobenzene using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for pentachlorobenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 2,125.

Inhalation

There is very little information concerning atmospheric exposure to QCB. The primary site for such exposure could be the workplace in industries utilizing and/or producing QCB.

Dermal

No information was obtained which concerns dermal exposure to pentachlorobenzene.

PHARMACOKINETICS

Absorption, Distribution, Metabolism, Excretion

Table 1 presents data from Parke and Williams (1960) on the metabolism of pentachlorobenzene by rabbits. It can be seen that a substantial portion of the oral dose was recovered in the gut contents three to four days after dosing. Except for the possibility of biliary secretion, which appears unlikely from the data obtained after a parenterally administered dose, it would appear that pentachlorobenzene is very poorly absorbed from the gastrointestinal tract. It is also evident that distribution favors deposition in the fat. Engst, et al. (1976c) administered QCB orally to rats at a dose of 8 mg/kg for 19 days. They identified 2,3,4,5-tetrachlorophenol and pentachlorophenol as the major urinary metabolites. They also detected 2,3,4,6-tetrachlorophenol "and/or" 2,3,5,6-tetrachlorophenol and unchanged QCB. They reported the presence of 1,3,5-trichlorobenzene in the liver. Kohli, et al. (1976b) described 2,3,4,5-tetrachlorophenol and pentachlorophenol as urinary metabolites of QCB in the rabbit. They were detected at yields of 1 percent each of the administered dose. The authors suggest that the dechlorination-hydroxylation step to the tetrachlorophenol derivative proceeds through an arene oxide step. Koss and Koransky (1977) reported pentachlorophenol and 2,3,4,5-tetrachlorophenol as metabolites of QCB in the rat.

TABLE 1

Disposition of Pentachlorobenzene in the Rabbit as
Percentage of Administered Dose†

Dose/Route mg/kg	Time After Dose (Days)	Urine		Feces	Gut Contents	Pelt	Depot Fat	Rest of Body	Un-changed	Other Hydro-carbons	Total Accounted For
		Tri- or Penta-Chlorophenol	Other Phenol								
0.5 p.o.	3	0.2	1	5	45	1	15	6	0	9	82
0.5 p.o.	4	0.2	1	5	31	5	9	5.5	0	21	78
0.5 s.c.	10	0.7	1	1.5	0.5	47*	22*	10	0	L2	85

†Source: Parke and Williams, 1960.
*Located mainly at site of injection.

However, they stated that the amount of pentachlorophenol recovered in the urine represented about 9 percent of the administered dose. Quantitively, this is substantially greater than the amounts of pentachlorophenol reported by Kohli, et al. (1976b) for the rabbit. Parke and Williams (1960) reported that less than 0.2 percent of the dose was recovered as pentachlorophenol in rabbit urine, also a substantial difference from that observed in the rat. Rozman, et al. (1979) found that biological half-life for QCB in rhesus monkeys to be two to three months. After 40 days, 10 percent of the total dose was excreted in the urine; of this, 58 percent was pentachlorophenol. After the same period, about 40 percent of the dose was excreted in the feces, 99 percent of which was unchanged QCB. These authors explained this as unabsorbed QCB that was secreted in bile into the GI tract. Ariyoshi, et al. (1975) reported that, in female Wistar rats intubated with QCB at 250 mg/kg for three days, the compound increased the liver content of cytochrome P450 and increased the activities of aminopyrine demethylase and aniline hydroxylase. Microsomal protein and phospholipids were also increased as was the activity of delta-aminolevulinic acid synthetase.

Further information on the biotransformation and accumulation properties of QCB can be obtained from a study reported by Villeneuve and Khera (1975) who studied the placental transfer of halogenated benzene in rats. They administered oral doses of QCB to pregnant rats on days 6 through 15 of gestation. It can be seen in Table 2 that the accumulation in the organs is disproportionate to the increasing dose, implying that at doses between

TABLE 2

Tissue Distribution of Pentachlorobenzene (ppm wet tissue)
Following Oral Administration to Pregnant Rats*

Dose g/kg)	Fat[a]	Liver[a]	Brain[a]	Heart[a]	Kidney[a]	Spleen[a]	Whole[a,b] Fetus	Fetal[c] Liver	Fetal[c] Brain
50	470±106	13.9±5.1	6.9± 1.2	6.2±1.0	6.0±1.1	4.5±1.1	9.65±1.3	4.37±0.69	3.08±0.55
100	824±116	18.1±2.0	12.0± 1.7	12.6±2.0	10.6±1.5	8.3±1.3	21.2 ±2.1	10.4 ±1.31	5.31±0.60
200	3350±331	91.1±6.6	62.5±10.2	57.5±9.6	43.5±2.6	46.2±8.1	55.1 ±6.7	40.4 ±6.02	20.5 ±2.64

*Source: Villeneuve and Khera, 1975.

[a] Represents the mean of 5 animals ± S.E.M.

[b] Represents the mean of two fetuses from 15 litters ± S.E.M.

[c] Represents the mean of five fetuses each from a different litter ± S.E.M.

100 and 200 mg/kg, elimination approaches zero order kinetic behavior. The ease of accumulation of the compound within the fetus is also evident. This will be discussed further below.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Goerz, et al. (1978), in a study of the comparative abilities of QCB and HCB to induce porphyria, administered a diet of 0.05 percent QCB to female adult rats for a period of 60 days. The treatment resulted in an increased urinary excretion of porphyrins by the HCB treatment, but none with the QCB treatment. It is uncertain from these experiments whether the dosage levels for QCB are adequate. Induction of experimental porphyria can be accomplished with all of the other chlorinated benzenes, and it would appear that a more detailed examination of pentachlorobenzene should be done before any final conclusions are made concerning its ability to induce porphyria. A survey of the literature has revealed no other published data on the acute, subchronic or chronic toxicity of QCB. The only exceptions to this are data which have been gathered in association with pharmacokinetic and teratologic studies, but on the basis of the number of animals utilized and the time of administration, these are not particularly useful for calculating criteria. For example, Khera and Villeneuve (1975) administered QCB in doses of 50, 100, and 200 mg/kg orally to pregnant rats during days 6 to 15 of gestation. The adult rats (20 in each group) did not display any "overt" signs of toxicity, though it is not certain whether the word "overt" refers to any particularly informative toxicological examination.

There are no other studies which describe the chronic toxicity of pentachlororbenzene.

Koss and Koransky (1977) have suggested that a major consideration in the toxicity of pentachlorobenzene is its biotransformation to pentachlorophenol. Considering that the findings by Rozman, et al. (1979) showing the half-life of pentachlorobenzene to be two to three months, and the urinary excretion of pentachlorophenol to be 6 percent of the administered dose, it is doubtful that over a period of 40 days a substantial quantity of pentachlorophenol would be made available to the system.

Synergism and/or Antagonism

The interaction of QCB with microsomal enzyme systems might result in effects on biotransformation and toxicity of drugs and other chemicals. However, there are no available data on synergistic or antagonistic effects.

Carcinogenicity, Mutagenicity, Teratogenicity

There is one report that alludes to the carcinogenicity of pentachlorobenzene in mice and the absence of this activity in rats and dogs (Preussman, 1975). This paper has not been evaluated due to difficulties in locating the source. When made available it will be evaluated as a possible basis for a criterion standard.

Teratogenicity studies with QCB have been reported by Khera and Villeneuve (1975). As indicated above, QCB at 50, 100, or 200 mg/kg in corn oil was administered by stomach tube to pregnant rats on days 6 to 15 of gestation. The authors did not interpret these data to demonstrate the teratogenicity of QCB. However, extra ribs are considered abnormal in fetal development. Table 3 represents findings resulting from Cesarean sections done on day 22 of pregnancy. The high dose of QCB produced an increased incidence of uni- or bilateral extra rib, as well as sternal defects consisting of unossified or nonaligned sternabrae with cartilagenous precursors present. The authors considered that the sternal defects suggested a retarded sternal development, and that these were related to a decreased mean fetal weight. At lower doses the sternal defects were not noted, but there was an increased incidence of extra ribs. The number of litters with one or more litter mates showing an anomalous rib number (14th and 15th combined), versus numbers of litters examined for each dose group, was 3/19 for 0 mg/kg, 14/19 for 50 mg/kg, 11/19 for 100 mg/kg, and 15/19 for 200 mg/kg, showing an apparent dose-related incidence.

No data have been found concerning the mutagenicity of QCB.

TABLE 3

Prenatal Data on Rats Dosed on Days 6 to 15 of Gestation with Pentachlorobenzene*

	Dose (mg/kg)			
	0	50	100	200
No. of rats pregnant at term	19	18	19	17
No. of live fetuses, mean	12.1	12.5	11.5	10.7
% fetal death, $\frac{(\text{dead} + \text{deciduomas})\ 100}{\text{total implants}}$	1.3	4.2	3.1	3.2
Fetal weight, g., mean	4.8	4.9	4.8	4.4
No. of fetuses examined for skeletal anomalies	127	129	122	100
Anomalies, type and incidence				
Extra ribs:				
uni	2	18	10	17
bilateral	2	10	11	46
Fused ribs				2
Wavy ribs	5	2		
Sternal defects	5	4		31
No. of fetuses examined for visceral defects	67	69	67	52
Runts	1	2		2
Cleft Palate		1		
Other defects				2

*Source: Khera and Villeneuve, 1975

CRITERION FORMULATION

Current Levels of Exposure

Morita, et al. (1975) examined levels of QCB in adipose tissue samples obtained from general hospitals and medical examiners' offices in central Tokyo. The samples were collected from a total of 15 people. By gas chromatography the authors found the residual level of QCB to range from 0.004 µg/g to 0.020 µg/g, with a mean value of 0.09 µg/g of fat. Lunde and Bjorseth (1977) examined blood samples from workers with occupational exposure to pentachlorobenzene and found that their blood samples contained higher levels of this compound than a comparable group of workers not exposed to chlorobenzenes.

Special Groups at Risk

A group at increased risk would appear to be those individuals exposed occupationally. Due to the persistence of the compound in the food chain, an increase in the body burden of QCB might be expected in individuals on high fish diets or diets high in agricultural products containing residues of PCNB spraying.

Basis and Derivation of Criterion

A survey of the QCB literature revealed no acute, subchronic or chronic toxicity data with the exception of the study by Khera and Villeneuve (1975). These authors found an adverse effect on the fetal development of embryos exposed *in utero* to pentachlorobenzene administered to the dams at 50 mg/kg on days 6 to 15 of gestation. This dose constitutes a low-observed-adverse-effect level (LOAEL). According to current guidelines, extrapolation from such data requires application of a safety factor of from

1 to 10. Since the observed effect was only suggestive of teratogenicity of QCB, a safety factor of 3 is applied. Because long-term toxicity data on humans are not available and the existing animal data are sparse, an additional safety factor of 1,000 is applied to the calculation of an acceptable daily intake (ADI) as follows:

$$\text{ADI} = \frac{70\text{ kg} \times 50\text{ mg/kg}}{3{,}000} = 1.17\text{mg/day}$$

The average daily consumption of water was taken to be 2 liters and the consumption of fish to be 0.0065 kg daily. The bioconcentration factor for QCB is 2,125.

Therefore:

$$\text{Recommended Criterion} = \frac{1.17}{2 + (2{,}125 \times 0.0065)} = 0.074\text{ mg/l (or} \sim 74\mu\text{g/l)}$$

The recommended water quality criterion for pentachlorobenzene is 74 µg/l. The criterion can alternatively be expressed as 85 µg/l if exposure is assumed to be from consumption of fish and shellfish alone.

REFERENCES

Ariyoshi, T., et al. 1975. Relation between chemical structure and activity. I. Effects of the number of chlorine atoms in chlorinated benzenes on the components of drug-metabolizing systems and the hepatic components. Chem. Pharm. Bull. 23: 817.

Balba, M.H. and J.G. Saha. 1974. Metabolism of Lindane-^{14}C by wheat plants grown from treated seed. Environ. Let. 7: 181.

Beck, J. and K.E. Hansen. 1974. Degradation of quintozene, pentachlorobenzene, hexachlorobenzene, and pentachloroaniline in soil. Pestic. Sci. 5: 41.

Borzelleca, J.F., et al. 1971. Toxicologic and metabolic studies on pentachloronitrobenzene. Toxicol. Appl. Pharmacol. 18: 522.

Burlingame, A.L. 1977. Assessment of the trace organic molecular composition of industrial and municipal wastewater effluents by capillary gas chromatography/real time high resolution mass spectrometry: A preliminary report. Ecotoxicol. Environ. Saf. 1: 111.

Dejonckheere, W., et al. 1974. Hexachlorobenzene (HCB) and other organochlorine pesticide residues analyses in pollard pellets, cattle feed, and animal feed. Rev. Agric. 27: 325.

Dejonckheere, W., et al. 1975. Problems posed by residues in quintozene and hexachlorobenzene in lettuce and witloof cultures. Rev. Agric. 28: 581.

Dejonckheere, W., et al. 1976. Residues of quintozene, its contaminants and metabolites in soil, lettuce and witloof chicory, Belgium, 1969-1974. Pestic. Monitor. Jour. 10: 68.

Engst, R., et al. 1976a. Hexachlorocyclohexane metabolites in human urine. Z. Gesamte Hyg. Ihre. Grenzgeb. 22: 205.

Engst, R., et al. 1976b. The metabolism of hexachlorobenzene (HCB) in rats. Bull. Environ. Contam. Toxicol. 16: 248.

Engst, R., et al. 1976c. The metabolism of lindane and its metabolites gamma-2,3,4,5,6-pentachlorocyclohexane, pentachlorobenzene, and pentachlorophenol in rats and pathways of lindane metabolism. Jour. Environ. Sci. Health, Part B, Bull: 95.

Engst, R., et al. 1977. The metabolism of lindane in a culture of mold and the degradation scheme of lindane. Chemosphere. 6: 401.

Goerz, G., et al. 1978. Hexachlorobenzene (HCB) induced porphyria in rats. Effect of HCB metabolites on heme biosynthesis. Arch. Dermatol. Res. 263: 189.

Greve, P.A. 1973. Pentachlorobenzene as a contaminant of animal feed. Meded. Fac. Landbouwwet Rijksuniv Gent. 38: 775.

Igarashi, H., et al. 1975. Studies on the metabolic degradation of pentachloronitrobenzene (PCNB). Part 3. Photodegradation of pentachlorothioanisole and pentachloronitrobenzene. Nogaku Kagaku. 3: 90.

Johnson, K. 1980. Memorandum to D.W. Kuehl. U.S. EPA. March 10.

Karapally, J.C., et al. 1973. Metabolism of lindane-^{14}C in the rabbit: Ether soluble urinary metabolites. Jour. Agric. Food Chem. 21: 811.

Kazama, M., et al. 1972. Chemical hygiene studies on organic halogen compounds. I. Transfer of chlorobenzenes into hen eggs. Tokyo Toritsu Eisei Kenkyusho Kenkya Nempo. 23: 93.

Khera, K.S. and D.C. Villeneuve. 1975. Teratogenicity studies on halogenated benzenes (pentachloro-, pentachloronitro-, and hexabromo-) in rats. Toxicology. 5: 117.

Kohli, J., et al. 1976a. Balance of conversion of carbon-14 labeled lindanes in lettuce in hydroponic culture. Pestic. Biochem. Physiol. 6: 91.

Kohli, J., et al. 1976b. The metabolism of higher chlorinated benzene isomers. Can. Jour. Biochem. 54: 203.

Koss, G. and W. Koransky. 1977. Pentachlorophenol in Different Species of Vertebrates after Administratin of Hexachlorobenzene and Pentachlorobenzene. In: K.R. Rao (ed.), Pentachlorophenol, Plenum Press, New York, p. 131.

Kujawa, M., et al. 1977. On the Metabolism of Lindane. In: S.H. Zaidi (ed.), Environmental Pollution and Human Health, Proc. 1st Int. Symp. p. 661.

Kwiatkowski, G.T., et al. 1976. Chloroaromatic ether amines. Jour. Poly. Sci. 14: 2649.

Lunde, G. 1976. Persistent and non-persistent fat soluble chlorinated compounds in marine organisms. Nordforsk, Miljoevardssekr., Publ., Org. Miljoegifter Vatten Nord. Symp. Vattenforsk, 12th. p. 337.

Lunde, G. and A. Bjorseth. 1977. Human blood samples as indicators of occupational exposure to persistent chlorinated hydrocarbons. Sci. Total Environ. 8: 241.

Lunde, G. and E.B. Ofstad. 1976. Determination of fat-soluble chlorinated compounds in fish. Z. Anal. Chem. 282: 395.

Mathur, S.P. and J.G. Saha. 1977. Degradation of lindane-^{14}C in mineral soil and in organic soil. Bull. Environ. Contam. Toxicol. 17: 424.

Mehendale, H., et al. 1975. Metabolism and effects of hexachlorobenzene on hepatic microsomal enzymes in the rat. Jour. Agric. Food Chem. 23: 261.

Morita, M., et al. 1975. A systematic determination of chlorinated benzenes in human adipose tissue. Environ. Pollut. 9: 175.

Parke, D.V. and R.T. Williams. 1960. Studies in detoxification LXXXI. Metabolism of halobenzenes: (a) Penta- and hexachlorobenzene: (b) Further observations of 1,3,5 trichlorobenzene. Biochem. Jour. 74: 1.

Preussmann. R. 1975. Chemical carcinogens in the human environment. Hand. Allg. Pathol. 6: 421.

Rautapaa, J., et al. 1977. Quintozene in some soils and plants in Finland. Ann. Agric. Fenn. 16: 277.

Rozman, K., et al. 1977. Longterm feeding study of hexachlorobenzene in rhesus monkeys. Chemosphere. 6: 81.

Rozman, K., et al. 1978. Chronic low dose exposure of rhesus monkeys to hexachlorobenzene. Chemosphere. 7: 177.

Rozman, K., et al. 1979. Metabolism and pharmacokinetics of pentachlorobenzene in rhesus monkeys. Bull. Environ. Contam. Toxicol. 22: 190.

Saha, J.G. and R.H. Burrage. 1976. Residues of lindane and its metabolites in eggs, chicks, and body tissues of hen pheasants after ingestion of lindane carbon-14 via treated wheat seed or gelatin capsules. Jour. Environ. Sci. Health Bull: 67.

Seidler, H., et al. 1975. Studies on the metabolism of certain insecticides and fungicides in the rat. Part IV. Distribution, degradation and excretion of carbon-14-labeled lindane. Nahrung. 19: 473.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stijve, T. 1971. Determination and occurrence of hexachlorobenzene residues. Mitt. Geb. Lebenmittelunters. Hyg. 62: 406.

Ten Berge, W.F. and M. Hillebrand. 1974. Organochlorine compounds in several marine organisms from the North Sea and the Dutch Wadden Sea. Neth. Jour. Sea Res. 8: 361.

Tu, C.M. 1976. Utilization and degradation of lindane by soil microorganisms. Arch. Microbiol. 108: 259.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency. Contract No. 68-01-4646.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, Calif. Final rep., Task II, Contract No., 68-01-3887.

Villeneuve, D.C. and K.S. Khera. 1975. Placental transfer of halogenated benzenes (pentachloro-, pentachloronitro-, and hexabromo-) in rats. Environ. Physiol. Biochem. 5: 328.

Yang, R.S.H., et al. 1975. Chromatographic methods for the analysis of hexachlorobenzene and possible metabolites in monkey fecal samples. Jour. Assoc. Off. Anal. Chem. 56: 1197.

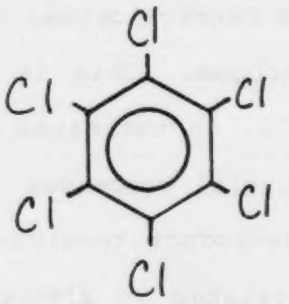
Yang, R.S.H., et al. 1978. Pharmacokinetics and metabolism of hexachlorobenzene in the rat. Jour. Agric. Food Chem. 26: 1076.

HEXACHLOROBENZENE

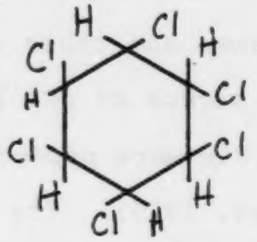
Mammalian Toxicology and Human Health Effects

INTRODUCTION

Hexachlorobenzene (HCB) is a crystalline substance which is virtually insoluble in water. It is used to control fungal diseases in cereals, and it is used in a number of organic syntheses. HCB should not be confused with the more commonly used insecticide benzene hexachloride (hexachlorocyclohexane).



HCB



benzene hexachloride

The main agricultural use of HCB is on wheat seed which is intended solely for planting. For this purpose, HCB is mixed with a blue dye, giving the treated wheat a distinct blue color. This coloration is intended as a warning that the seed has been treated with a poison and must not be used for stock or human consumption. In 1971, about 6,800 kg were used in the United States as a seed fungicide, its only registered use (Isensee, et al. 1976). Despite advice and regulations, treated seed grain has been fed to animals intended for, or whose products are intended for human consumption. HCB does not degrade easily under normal conditions. Trace amounts have been found in areas and ecological systems far removed from the original area of application. HCBs impact on agriculture as a result of environmental contamination may be much larger than its utility as a fungicide to control smut diseases in cereal grains. Foodstuffs such as eggs, milk, and meat become contaminated with HCB as a result of ingestion of HCB-treated cereals by livestock.

Commercial production of HCB in the United States was discontinued in 1976 (Chem. Econ. Hdbk., 1977). However, even prior to 1976, most HCB was produced as a waste by-product during the manufacture of perchloroethylene, carbon tetrachloride, trichloroethylene, and other chlorinated hydrocarbons. This is still the major source of HCB in the U.S. In 1972, an estimated 2.2×10^6 kg of HCB were produced from these industrial processes (Mumma and Lawless, 1975). Its generation as a by-product remains unabated. HCB found in Louisiana was apparently related to airborne industrial emissions, while residues in sheep from Texas and California were traced to pesticide contaminated with HCB. Until recently, HCB was a major impurity in the herbicide dimethyl tetrachloroterephthalate and the fungicide pentachloronitrobenzene. HCB has been found in polyethylene plastic bottles from one source (Rourke, et al. 1977). HCB is used in industry as a plasticizer for polyvinyl chloride as well as a flame retardant.

EXPOSURE

Ingestion from Water

Very little is known regarding potential exposure to HCB as a result of ingestion of contaminated water. HCB has been detected in specific bodies of water, particularly near points of industrial discharge. Except for such source-directed sampling, there is little information of HCB concentrations in surface waters. HCB has been found in river water and soil samples collected in the vicinity of an industrialized region bordering the Mississippi River between Baton Rouge and New Orleans, Louisiana. The levels of HCB in the Mississippi River water samples were low, usually below 2 µg/kg. Maximum concentrations of HCB were found in samples of levee soil collected near Plaquemine (400 µg/kg) and of ditch mud collected near Darrow (874 µg/kg). Soil on the river side of the levee accumulated HCB from the load carried in solution and in suspension in the river water (Laska, et al. 1976). High concentrations of HCB were sporadically found in a newly dug pond near a landfill where wastes containing HCB were buried and in a small stream carrying runoff water from a field adjacent to an industrial plant. The HCB levels in the landfill pond water varied from 4.8 to 74.9 µg/kg and from 10,500 to 53,130 µg/kg in mud samples. The HCB levels in the stream water varied from 0.1 to 72.8 µg/kg and from 2,520 to 13,800 µg/kg in mud samples (Laseter, et al. 1976).

Water samples from western Lake Superior contained HCB; the exact concentration was not quantitively measured. Lake Superior is one of the largest and cleanest oligotrophic bodies of fresh water in the world. The total population density around the lake is low and the concentrations of trace elements have remained relatively small compared to those in other Great Lakes (Veith, et al. 1977). HCB was detected in drinking water supplies at three locations, at concentrations ranging from 6 to 10 ng/kg. HCB was detected in finished drinking water at two locations, at concentrations ranging from 4 to 6 ng/kg (U.S. EPA, 1975).

HCB has considerable potential to bioaccumulate in the aquatic environment and is very persistent. The combination of these two attributes makes HCB a potentially hazardous compound in the environment. Soil contaminated with HCB would retain HCB for many years. If contaminated soil finds its way into the aquatic environment, it will become available to aquatic organisms.

HCB enters the environment in the waste streams from the manufacture of chlorinated hydrocarbons and from its agricultural use as a pre-emergence fungicide for small grains. HCB becomes redistributed throughout the environment as a consequence of its leaching from industrial waste dumps and its volatilization from industrial sources and contaminated impoundments. HCB adsorbed to soil may be transported long distances in streams and rivers. HCB is now distributed throughout the world. The solubility of HCB in water is low, however, its concentration in water rarely exceeding 2 µg/kg.

HCB is sufficently volatile so that one air drying of moist soil or biological samples causes a 10 to 20 percent loss of HCB (vapor pressure 1.089×10^{-5} mm Hg at 20°C). The half-life of HCB in soil (incorporated at 10 kg/ha) stored in plastic-covered plastic pots is about 4.2 years (Beck and Hansen, 1974). HCB is not lost from soil 2 to 4 cm beneath the surface during 19 months, but 55 percent is lost from the surface 2 cm of soil within two weeks (Beall, 1976). Clearly, volatilization is a significant factor in the loss of HCB from soil and for its entry into the atmosphere. No HCB is lost from soil treated with 0.1 to 100 mg/kg of HCB and stored under aerobic (sterile and nonsterile) and anaerobic nonsterile conditions for one year in covered containers (Isensee, et al. 1976). Degradation products of HCB have not been found in plants and soil. Hexachlorobenzene is relatively resistant to photochemical degradation in water. Photolysis of HCB occurs slowly in methanol, 62 percent being degraded in 15 days. It is not known whether organic matter in natural waters or natural photosensitizers in the environment can enhance the rate of degradation of HCB (Plimmer and Klingebiel, 1976). HCB may be even more stable than DDT or dieldrin in the environment (Freitag, et al. 1974). HCB has been singled out as the only organic chemical contaminant present in the ocean at levels likely to cause serious problems (National Academy of Sciences (NAS), 1975).

HCB, adsorbed to soil or sand, is released into water and taken up by aquatic organisms such as algae, snails, daphnids (Isensee, et al. 1976), and fish (Zitko and Hutzinger, 1976). The alga, Chara, collected from the lower Mississippi River (Louisiana) contained HCB at 563 µg/kg wet weight. An undefined plankton sample contained 561 µg HCB/kg (Laska, et al. 1976).

The aquatic plants Najas and Ellocharios contained 147 µg HCB/kg and 423 µg HCB/kg wet weight, respectively (Laseter, et al. 1976). Three aquatic invertebrate genera: snail, Physa, crayfish Procambarus, and dragonfly larvae, Anisoptera, also collected from the lower Mississippi River, contained 294 µg/kg, 48.67 µg/g, and 4.7 µg/g, respectively (Laseter, et al. 1976). The HCB levels in inland fish from the United States ranged from "none detected" to 62 mg HCB/kg. The high mean level of HCB in carp (16 mg/kg) was attributed to runoff from an industrial chemical storage area. The mean HCB concentration in seven other inland fish ranged from <1 to 130 µg/kg (Johnson, et al. 1974). The HCB level in fish collected from the contaminated lower Mississippi River ranged from 3.3 to 82.9 mg/kg for fish. The HCB levels in mosquitofish collected some distance from the site of the HCB industrial source on the lower Mississippi River ranged from 71.8 to 379.8 µg/kg, about 100-fold lower than the HCB content in fish near the site of industrial contamination (Laseter, et al. 1976).

Marine invertebrates collected from the central North Sea contained substantially less HCB than invertebrates from the central contaminated lower Mississippi River (Schaefer, et al. 1976). Residues of HCB were determined in 104 samples of marine organisms collected at various sites off the Atlantic Coast of Canada during 1971 and 1972. The results indicated a widespread, low-level distribution of HCB (<1 to 20 µg HCB/kg). The highest levels of HCB were in fatty samples (1 µg/kg in whole cod vs 39 µg/kg in cod liver; none detected in whole lobster vs 54 µg/kg in lobster hepatopancreas). Herring contained the greatest whole body burden of HCB (20 µg/kg) (Sims, et al. 1977). The HCB levels in marine fish from the central North Sea ranged from 0.2 to 2.9 µg/kg for muscle and from 2.9 to 10 µg/kg for liver. The organ concentrations of HCB increased with increasing lipid content of the organ (Schaefer, et al. 1976).

HCB has been detected in a number of water and land birds. Carcasses of immature ducks contained HCB ranging from >60 to 240 µg/kg (White and Kaiser, 1976). The HCB levels ranged from 110 to 500 µg/kg in carcasses of 4 of 37 bald eagles (Cromartie, et al. 1975). The HCB levels in the eggs of the common tern, Sterna, ranged from 1.35 to 14.7 mg/kg dry weight (Gilbertson and Reynolds, 1972). Eggs of double-crested cormorants, Phalacrocorax, from the Bay of Fundy were monitored from 1973 to 1975. The eggs contained 15 to 17 µg HCB/kg wet weight (Zitko, 1976).

Foxes and wild boars, which feed on small animals such as mice and invertebrates, accumulated large amounts of HCB. Because predators and scavengers contain higher residues of HCB than herbivores, it would seem that biomagnification through the food chain is occurring (Koss and Manz, 1976).

Ingestion from Food

Ingestion of excessive amounts of HCB has been a consequence of carelessness, lack of concern, and ignorance. There is a tendency to dispose of excess wheat seed by feeding it to stock without due recognition of the toxic properties of the compounds concerned. In the mid-1960's, a shipment of Australian powdered eggs was rejected for importation into the United States by the Food and Drug Administration on the grounds of contamination with HCB. The New South Wales Egg Marketing Board tests samples of eggs that it handles and will not accept for distribution any eggs which contain significant amounts of HCB.

Food materials were collected at retail and department stores in Tokyo, Japan, and were weighed in the amounts consumed a day. The food materials were classified into four categories: cereals, vegetal products (vegetables, vegetal oils, seasoning, and seaweed), marine animal products, and terrestrial animal products including dairy products and eggs. The dietary intake of HCB ranged from 0.3 µg/day to 0.8 µg/day. Contributions from cereals were low (<0.05 µg/day). The contribution from vegetal products ranged from <0.05 µg/day to 0.4 µg/day; that for marine animal products from <0.05 µg/day to 0.3 µg/day; and that for terrestrial animal products from 0.3 µg/day to 0.4 µg/day (Ushio and Doguchi, 1977).

Herds of cattle in Louisiana were condemned by the State Department of Agriculture in 1972 for excessive HCB residues, that is, they exceeded 0.3 mg HCB/kg in fat. Levels as high as 1.52 mg HCB/kg were reported. Of 555 animals tested among 157 herds, 29 percent of the cattle sampled contained <0.5 mg HCB/kg in fat. HCB residues apparently did not arise from agricultural application of HCB fungicide but from contamination of air, soil, and grass by industrial sources (U.S. EPA, 1976). In a total diet study conducted in Italy between 1969 and 1974, the average intake was estimated to be 4.2 µg/person/day (Leoni and D'Arca, 1976). HCB contents of various foods can be found in Table 1. In an effort to reduce the amount of HCB entering the environment, the Federal Republic of Germany no longer allows application of HCB-containing pesticides (Geike and Parashar, 1976). The New South Wales Department of Health (Australia) has recommended that the concentration of HCB in eggs must not exceed 0.1 mg/kg (Siyali,

TABLE 1

Hexachlorobenzene Content of Food (μg HCB/kg)*

(Italy: 1969 - 1974)

Food	Mean	Range
Bread	1.1	n.d.(a) - 2.9
Noodles	0.7	0.2 2.9
Maize flour	n.d.	
Rice	0.8	0.3 - 1.1
Preserved legumes	1.1	n.d. - 3.1
Dry legumes	2.4	0.2 - 5.1
Fresh legumes	n.d.	
Fresh vegetables and artichokes	0.5	n.d. - 1.8
Tomatoes	n.d.	-
Potatoes	n.d.	-
Onions	0.6	0.6 - 0.6
Carrots and other root vegetables	n.d.	-
Fresh fruit	n.d.	-
Dried fruit	n.d.	-
Exotic fruit	n.d.	-
Citrus fruit	n.d.	-
Bovine meat	0.7 (33.6)	n.d. - 1.4 - (78.4)
Mutton, game and rabbits	1.0 (25.4)	n.d. - 2.6 - (51.3)
Giblets	0.7 (27.0)	n.d. - 1.3 - (53.9)
Pork meat	25.0 (96.3)	9.1 - 40.9 (74.3) -(118.3)
Chicken	5.7 (49.0)	n.d. - 11.5 - (75.0)
Eggs	4.7	1.7 - 7.5
Fresh fish	0.7	n.d. - 1.8
Preserved fish	n.d.	
Whole milk	4.1	0.2 - 17.2
Butter	133.0	-
Cheese	12.6 (63.0)	n.d. - 25.1 -(126.0)
Olive oil	13.1	n.d. - 53.8
Seed oil	4.7	n.d. - 27.9
Lard	46.2 63.4	-
Wine	0.1	n.d. - 0.6
Beer	n.d.	-
Sugar	0.2	n.d. - 0.6
Coffee	n.d.	-

Values in parentheses are for extracted fat.

(a) n.d. -- not detected

*Source: Adapted from Leoni and D'Arca, 1976.

1973). The National Health and Medical Research Council (NHMRC) (Australia) has set the tolerance for cows' milk at 0.3 mg HCB/kg in fat (Miller and Fox, 1973). The Louisiana Department of Agriculture has set the tolerance for meat at 0.3 mg HCB/kg in fat (U.S. EPA, 1976).

There is a substantial body of information on HCB levels in human milk for a number of countries. In the United States, human milk contained a mean concentration of 78 ppb (Savage, 1976). Milk from 45 women living in a metropolitan area (Sydney, Australia) was found to contain HCB. The mean HCB concentration in human milk was 15.6 µg/kg, and 7 percent of the samples contained 51 to 100 µg HCB/kg. In addition, 49 human milk samples from France and 50 from the Netherlands contained HCB, but no concentrations were reported. Human milk samples from Germany contained 153 µg HCB/kg of whole milk and those from Sweden 1 µg/kg (Siyali, 1973). HCB was also detected in all of 40 human milk samples from Brisbane, Australia, and a rural area (Mareeba on the Atherton Tablelands). The excretion of HCB into human milk was higher in Brisbane samples than in Mareeba samples (2.22 versus 1.23 mg HCB/kg in milk fat). The higher levels of HCB in Brisbane donors may be related to the close proximity to a major grain growing area, the Darling Downs. The daily intake of HCB by infants in Brisbane was estimated to be 39.5 µg per day per 4 kg of body weight and in Mareeba to be 14 µg per day per 4 kg of body weight. The calculated average daily intake of HCB by breast-fed babies in both areas exceeded the acceptable daily intakes of 2.4 µg/kg/day recommended by the Food and Agriculture Organization/World Health

Organization (FAO/WHO) (1974). The HCB content of human milk also exceeded the Australian NHMRC tolerance for cows' milk (0.3 mg/kg in milk fat). The dietary intake by young adults (15-to-18-year old males) was estimated to be 35 µg HCB per person per day (Miller and Fox, 1973). Similarly, HCB was found in all of 50 samples of human breast milk collected in Norway. The mean HCB level was 9.7 µg/kg, with a maximum value of 60.5 µg/kg. The HCB content of colostrum (7.7 µg/kg) was within the range of that for milk 1 to 16 weeks after birth (5.9 to 10.0 µg/kg). The HCB content of the human milk samples in this survey exceeded the maximum concentration of 20 µg/kg for cows' milk approved by FAO/WHO. The milk sample with the highest HCB level exceeded this standard by three-fold (Bakken and Seip, 1976).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCF for a lipid-soluble compound in the tissues of various aquatic animals seems to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States was analyzed by SRI International (U.S. EPA, 1980a). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 22,000 was obtained for hexachlorobenzene using fathead minnows (U.S. EPA, 1980b). These fathead minnows probably contained about 7.6 percent lipids (Veith, 1980). An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average bioconcentration factor for hexachlorobenzene and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 22,000 x 0.395 = 8,690.

Inhalation and Dermal

HCB enters the air by various mechanisms such as release from stacks and vents of industrial plants, volatilization from waste dumps and impoundments, intentional spraying and dusting, and unintentional dispersion of HCB-laden dust from manufacturing sites, during transport of finished material or wastes, and by wind from sites where HCB has been applied. Plasma HCB concentrations of 86 individuals living in Louisiana adjacent to a plant producing chlorinated solvents, but not occupationally exposed, averaged 3.6 µg/kg with a maximum of 23 µg/kg. Plasma HCB concentrations were higher in males than in females (4.71 µg/kg compared with 2.79 µg/kg, respectively), but there was no significant difference between age groups. There was no evidence of cutaneous porphyria in this population, but persons with high plasma concentrations of HCB showed elevated coproporphyrin and lactic dehydrogenase levels. Only two of 48 household meals sampled contained significant quantities of HCB, but there was some correlation between concentration in plasma and the concentration of HCB in household dust. Some household dust contained as much as 3.0 mg/kg. Affected households were on the route of a truck which regularly carried residues containing HCB from a factory to a dump. Workers in the adjacent plant engaged in manufacturing carbon tetrachloride and perchloroethylene had plasma HCB concentrations from 14 to 233 µg/kg (Burns and Miller, 1975).

Pest control operators in their day-to-day work handle a variety of toxic chemicals, including chlorinated hydrocarbon pesticides. Pesticides may enter the body by inhalation of spray mist which exists in confined spaces. The levels of HCB in blood of pest control operators in New South Wales, Australia, were found to be elevated in a 1970-1971 study (1 to 226 µg/kg). The pest control operators seldom used respirators, and those in use appeared to be ineffective due to poor service maintenance. The respiratory exposure values were many-fold higher than the acceptable daily intake as applied to food by WHO (0.1 µg/kg/day or 7 µg/day intake for a 70 kg man) (Simpson and Shandar, 1972).

HCB may enter the body by absorption through the intact skin as a result of skin contamination. Workers involved in the application or manufacture of HCB-containing products are, therefore, at greater risk.

HCB enters the body as a result of ingestion and presumably by inhalation and absorption through the skin. HCB remains in the blood for only a short period before it is translocated to fatty tissues or is excreted. HCB blood levels reflect either recent exposure or mobilization of HCB from body fat depots. HCB finds its way into air, water, and food as a result of unintentional escape from industrial sites, intended application of HCB containing products, volatilization from waste disposal sites and impoundments, and unintentional dispersion during transport and storage. The result has been the worldwide dissemination of HCB and ubiquity in man's food, at least in low levels.

All blood samples taken from children (1 to 18 years old) in upper Bavaria in 1975 contained HCB at 2.6 to 77.9 µg/kg. The study included 90 males and 96 females. HCB levels in blood showed a positive, hyperbolic correlation with age, tending to an upper limit of 22 µg/kg for boys and 17 µg/kg for girls. The rate of increase in HCB concentration was inversely proportional to a function of age. A substantial accumulation of HCB became evident 9 to 10 months after birth (Richter and Schmid, 1976). HCB was found in all of a series of human fat samples collected from autopsy material throughout Germany. The highest levels of HCB were in specimens from Munster (22 mg HCB/kg in fat) and Munich (21 mg HCB/kg in fat) (Acker and Schulte, 1974). The presence of HCB in Japanese adipose tissue obtained at autopsy was determined for a total of 241 samples from Aichi Cancer Center Research

Institute, Chikusa-Ka Nagoya, Japan. The concentration of HCB in these fat samples was 90 µg/kg ± 6 µg/kg standard error (Curley, et al. 1973).

HCB was found in all of 75 specimens of Australian human body fat (1.25 mg/kg). Perirenal fat was taken at autopsy from a random selection of bodies at the City Morgue, Sydney, Australia. All ages and both sexes were included in the study (Brady and Siyali, 1972). The incidence (63 percent of samples tested) and concentration of HCB (0.26 mg/kg) in 38 specimens of human body fat from Papua and New Guinea were lower than the Australian values. The concentration of HCB in whole blood of 185 people who had some occupational exposure to organochlorine compounds in their working conditions and of 52 who had no known exposure was determined. None of the subjects displayed apparent signs of intoxication. Over 95 percent of the subjects had HCB in their blood. The HCB blood level in the exposed population was 55.5 µg/kg, with 9 percent having more than 100 µg/kg. The HCB blood level in the population with no known exposure was 22 µg/kg, with none having as much as 100 µg/kg. Levels of 50 to 100 µg/kg whole blood indicate either recent exposure over and above that normally assimilated from the environment or the mobilization of fat depots associated with a loss in total body weight. The mean HCB level in 81 samples of human body fat was 1.31 mg/kg, with a maximum of 8.2 mg/kg. All 81 human fat samples contained HCB (Siyali, 1972).

The HCB levels in adipose tissue of Canadians, collected in 1972 by Burns and Miller (1975), were determined. The regional distribution of the samples was as follows: 16 from the eastern region (Newfoundland, Prince Edward Island, Nova Scotia and New Brunswick), 50 from Quebec, 57 from Ontario, 22 from the central region (Manitoba and Saskatchewan) and 27 from the western region (Alberta and British Columbia). All of the adipose samples contained HCB, with an overall mean value of 62 µg/kg. HCB values were lowest in the samples from the eastern (25 µg/kg) and central (15 µg/kg) regions and highest in Quebec (107 µg/kg). The Ontario samples averaged 60 µg HCB/kg and those from the western region 43 µg/kg. The HCB content of adipose tissue from females (82 µg/kg) was greater than that for males (52 µg/kg). The HCB content of human adipose tissue did not show an age-related trend: 0 to 25 years, 76 µg/kg; 26 to 50 years, 45 µg/kg; and 51+ years, 70 µg/kg (Mes, et al. 1977). In the study of Richter and Schmid, the age-related accumulation of HCB was marked only for the first five years of life (Richter and Schmid, 1976). Plasma HCB levels in a Louisiana population exposed through the transport and disposal of chemical waste containing HCB averaged 3.6 µg/kg in a study of 86 subjects. The highest level was 345 µg/kg in a sample from a waste disposal worker, while the highest level in a sample from a member of the general population was 23 µg/kg (Burns and Miller, 1975).

PHARMACOKINETICS

Absorption

To date, only absorption of HCB from the gut has been examined in detail. Fish fed HCB-contaminated food take up the material in a reasonably direct relationship to the concentration in the food (Sanborn, et al. 1977). Intestinal absorption of HCB from an aqueous suspension was poor in both rabbits (Parke and Williams, 1960) and rats (Koss and Koransky, 1975). The amount of HCB left in the intestinal contents 24 hours after administration was small. Intestinal absorption of HCB by rats was substantial when the chemical was given in cotton seed oil (Albro and Thomas, 1974) or olive oil (Koss and Koransky, 1975). Between 70 percent and 80 percent of doses of HCB ranging from 12 mg/kg to 180 mg/kg were absorbed. The fact that HCB is well absorbed when dissolved in oil is of particular relevance for man. HCB in food products will selectively partition into the lipid portion, and HCB in lipids will be absorbed far more efficiently than that in an aqueous media. This is consistent with the observation that the highest HCB levels ever observed have been in tissues of carnivorous animals (Acker and Schulte, 1971; Koeman, 1972). HCB is readily absorbed from the abdominal cavity after intraperitoneal injection of the chemical dissolved in oil.

Data of toxicological experiments should take into account how HCB was administered. Relatively little HCB was absorbed by the walls of the stomach and duodenum of rats one hour after oral administration of HCB suspended in aqueous methylcellulose. After three hours, the ingested HCB reached the jejunum and ileum, resulting in increasing concentrations in the walls of these parts of the intestine. Liver and kidney contained some HCB; however, the concentrations in lymph nodes and adipose tissue were much higher. During the remaining 45 hours, the concentrations in liver and kidney decreased, whereas those in lymph nodes and adipose tissue remained relatively constant or rose slightly. Portal venous transport to the liver seemed to be a minor pathway because, in spite of its slow metabolism, HCB never achieved high concentrations in the liver. The majority of the ingested HCB was absorbed by the lymphatic system in the region of the duodenum and jejuno-ileum, and deposited in fat, bypassing the systemic circulation and excretory organs. There appears to be an equilibrium between lymph nodes and fat (Iatropoulos, et al. 1975).

Distribution

It is well known that HCB has a low solubility in water (6 µg/kg) (Lu and Metcalf, 1975) and a high solubility in fat (calculated log partition coefficient in octanol/H_2O=6.43). Accordingly, the highest concentrations of HCB are in fat tissue (Lu and Metcalf, 1975). The concentration of HCB in fish fed contaminated food (100 mg/kg) for three days was 4.99 mg/kg in liver and 1.53 mg/kg in muscle (Sanborn, et al. 1977). The concentration of HCB in Japanese quail fed contaminated food (5 mg/kg) for 90 days was 6.88 mg HCB/kg in liver and 0.99 mg/kg in brain of female birds and 8.56 mg/kg in liver and 1.44 mg/kg in brain of male birds (Vos, et al. 1971). As noted above, HCB accumulated in fatty tissues. After prolonged feeding of a constant level of HCB, the concentration of compound in the fat of laying hens reached a plateau. This indicates that an equilibrium between uptake and excretion can be achieved. This phenomenon allows one to calculate the ratio of the concentration of HCB in fat to the concentration in the feed. This accumulation or storage ratio apparently is independent of HCB concentration in the feed over a wide range. The accumulation ratio for HCB in laying hens is about 20 (Kan and Tuinstra, 1976).

The distribution of HCB in rat tissues was similar for animals given a single oral dose or a single intraperitoneal injection of HCB dissolved in olive oil. Adipose tissue contained about 120-fold, liver, 4-fold; brain, 2.5-fold; and kidney, 1.5-fold more HCB than muscle. The HCB content of adrenals, ovaries and the Harderian gland was essentially the same as skin, whereas that for heart, lungs, and intestinal wall corresponded to the level in liver. The thymus content was similar to that of brain (Koss and Koransky, 1975).

The distribution of HCB in mice fed a diet containing 167 mg HCB/kg was determined after three and six weeks. The HCB level in the serum was 23 mg/kg after three weeks and 12 mg/kg after six weeks; for liver, 68.9 mg/kg after three weeks and 56 mg/kg at six weeks; for spleen, 20.9 mg/kg at three weeks and 47 mg/kg at six weeks; for lung, 85.1 mg/kg at three weeks and 269 mg/kg at six weeks; and for the thymus, 48.6 mg/kg at three weeks and 152 mg/kg at six weeks. The only histological alterations seen in tissues of mice fed HCB for six weeks was a centrilobular and pericentral hepatic parenchymal cell hypertrophy; hepatic Kupffer cells appeared normal in number and morphology (Loose, et al. 1978).

Adipose tissue serves as a reservoir for HCB, and depletion of fat depots results in mobilization and redistribution of stored pesticide. For example, food restriction caused mobilization of

HCB stored within the fat depots of rats that had been fed HCB-contaminated food for 14 days. Although HCB was redistributed into the plasma and other tissues of the body, food restriction did not increase the excretion of HCB; therefore, the total body burden was not reduced. Rats receiving 100 mg HCB/kg/day orally for 14 days developed tremors, lost appetite, and some died during subsequent food restriction. Weight loss from whatever cause results in redistribution of HCB contained in adipose tissue, and if the initial level of the pesticide is sufficiently high, toxic manifestations may develop (Villeneuve, 1975).

Metabolism

Although HCB appears to be relatively stable in the soil, it is metabolized by a variety of animal species. About half of HCB taken into the body of fish fed contaminated food is converted into pentachlorophenol (Sanborn, et al. 1977). The rabbit does not appear to oxidize HCB to pentachlorophenol (Kohli, et al. 1976). In rats given HCB intraperitoneally on two or three occasions (total dose 260 to 390 mg HCB/kg), pentachlorophenol, tetrachlorohydroquinone, and pentachlorothiophenol were the major metabolites in urine. More than 90 percent of the radiolabeled HCB material in the urine had been metabolized, whereas only 30 percent of the starting radiolabeled HCB material in the feces was metabolized. Of the HCB administered intraperitoneally, 65 percent was in the animal body (almost all as HCB), 6.5 percent was excreted in the urine (mostly as metabolites) and 27.2 percent was excreted in the feces (about 70 percent as HCB). The metabolites in feces were (in decreasing order) pentachlorophenol > pentachlorothiophenol > an unidentified substance (Koss, et al. 1976).

In organs of rats given 8 mg HCB/kg dissolved in sunflower oil by gavage, only HCB, pentachlorobenzene, and pentachlorophenol could be identified. The metabolites were present in small concentrations. The HCB level in fat was 83 mg/kg, in muscle, 17 mg/kg; in liver, 125 µg total; in kidneys, 21 µg each; in spleen, 9 µg total; in heart, 1.5 µg total and in adrenals, 0.5 µg each. In urine, the main metabolites of orally administered HCB were pentachlorophenol, tetrachlorophenol, trichlorophenol, and pentachlorobenzene. Small amounts of trichlorophenol and tetrachlorophenol were present as glucuronide conjugates. The feces contained a little pentachlorobenzene, but mostly the parent HCB (Engst, et al. 1976).

HCB in corn oil given orally to rats at a dose of 20 mg/kg for 14 days caused an elevation of the levels of cytochrome P-450 and NADPH-cytochrome c reductase activity. HCB appears to be an inducer of the hepatic microsomal system of the phenobarbital type (Carlson, 1978). In a separate study, the cytochrome P-450 level was elevated in rats (Porton strain) fed HCB mixed into the diet (dose about 19 mg/kg) for 14 days, but not in rats (Agus strain) fed food containing HCB for 90 days. In both HCB-exposed groups, benzo(a)pyrene hydroxylation activity was elevated, but aminopyrine N-demethylatse activity was not significantly enhanced. It has been proposed that HCB is an inducer of hepatic microsomal enzyme activity having properties of both the phenobarbital type and the 3-methylcholanthrene type (Stonard, 1975; Stonard and

Greig, 1976). Although HCB is a well-documented inducer of hepatic microsomal enzyme activity, the hexobarbital sleeping times of rats fed 2,000 mg HCB/kg/day for 14 days were the same as unexposed control rats. The duration of hexobarbital-induced sleep decreased 14 days after eliminating HCB from the diet. In rats fed 500 mg HCB/kg/day for 14 days, hepatic glucose-6-phosphatase activity was decreased and serum isocitrate dehydrogenase activity remained undetectable. In rats fed 10 mg HCB/kg/ day for 14 days, the liver was enlarged; the cytochrome P-450 level, detoxification of EPN, O-ethyl O-(p-nitrophenyl) phenylphosphonothioate, benzpyrene hydroxylase activity and azoreductase activity were increased, whereas cytochrome c reductase and glucuronyl transferase activities were unaltered.

Excretion

As described in earlier sections, HCB is excreted mainly in the feces and to some extent in the urine in the form of several metabolites that are more polar than the parent HCB. Usually a plateau is reached in most tissues when the dose is held relatively constant. If exposure increases or decreases, however, the body concentration will increase or decrease, accordingly.

Fish fed HCB contaminated food (100 mg/kg) for three days have relatively high levels of HCB and pentachlorophenol in their stomach (27.16 mg/kg and 19.14 mg/kg, respectively) and intestine (26.82 mg/kg and 15.94 mg/kg, respectively) by the fourth day. The half-life of HCB in the stomach, intestine, and muscle was 8 to 8.5 days, in the carcass 10 days, and in the liver 19.6 days. During the initial elimination period, the clearance of HCB from the intestine and muscle lagged behind that for the stomach and liver, and may indicate biliary excretion with enterohepatic recirculation (Sanborn, et al. 1977), which has been described in dogs (Sundlof, et al. 1976).

HCB accumulates in the eggs of laying hens fed contaminated food. The accumulation ratio (level of HCB in whole egg/level in the feed) was 1.3. The actual HCB concentration in eggs was 20 µg/kg for hens fed 10 µg HCB/kg of feed and 140 µg/kg for hens fed 100 µg HCB/kg. Although the concentration of HCB in eggs is usually viewed from the perspective of accumulation in a human food, it can also be regarded as an excretion process. Whereas 10 percent of the daily HCB intake is excreted in the feces, 35 percent is excreted in the eggs of laying hens (Kan and Tuinstra, 1976). The rate of elimination of HCB from swine was greatest 48 to 72 hours after a single intravenous injection of drug. The rate of release of HCB from fat was the rate limiting factor for excretion at later times. Half of the starting HCB material in the feces was unmetabolized HCB. All of the HCB material excreted in the urine were metabolites of HCB. Excretion of HCB from swine was 5-fold to 10-fold slower than excretion from dogs (Wilson and Hansen, 1976).

Clearance of HCB from brain of rats given a single injection intraperitoneally occurs in two steps: a slow phase on days 1 to 14, and a very slow phase thereafter. The half-life for the slow phase was 10 days and that for the very slow phase was 57 days. Similarly, the half-life of HCB in testes was 15 days for the initial slow clearance and 62 days for the later very slow phase.

The initial clearance rates (half-lives) for the heart, lung and kidney were 15, 13, and 16 days respectively. In contrast to the pattern for individual organs, the clearance of HCB from the whole body proceeded as a single step process, with a half-life of 60 days. The initial clearance of HCB from individual organs therefore reflects a redistribution of the chemical among the tissues of the body (Morita and Oishi, 1975). Clearance of HCB from organs of rats given a single dose of HCB dissolved in olive oil by gavage also occurred in two stages: a very slow phase between days two and five, or eight, and a slow phase thereafter. The overall half-life of HCB for fat, skin, liver, brain, kidney, blood, and muscle was 8 to 10 days. The administered chemical was retained in the tissue as unaltered HCB. During a two week period, 5 percent of the administered HCB was excreted in the urine; essentially all as metabolites of HCB, and 34 percent was excreted in the feces, mostly as unaltered HCB. The fecal excretion of a fairly high amount of unmetabolized HCB is presumed to be due to biliary secretion. Unchanged HCB has been detected in bile of rats after intraperitoneal administration of the chemical (Koss and Koransky, 1975).

No radioactivity was detected in the expired air of rats administered radiolabeled HCB (Koss and Koransky, 1975).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Japanese quail are among the most sensitive species to HCB. Japanese quail fed a diet containing 5 mg HCB/kg for 90 days developed enlarged livers, had slight liver damage and excreted increased amounts of coproporphyrin in the feces. Increased excretion of coproporphyrin was noticeable after 10 days (Vos, et al. 1971).

The acute toxicity of HCB for vertebrates is low: 500 mg/ kg intrapertioneally is not lethal in rats; the lethal oral dose in guinea pigs is greater than 3 g/kg; and the lethal oral dose in Japanese quail is greater than 1 g/kg (Vos, et al. 1971). In acute studies, HCB was more toxic for guinea pigs than rats, but accumulated to a lesser degree in the guinea pig. Male rats appeared to be more susceptible to HCB than females (Villeneuve and Newsome, 1975). HCB is able to induce rat microsomal liver enzymes; HCB was more effective in stimulating aniline hydroxylase than aminopyrine demethylase or hexobarbital oxidase. HCB is not a particularly effective inducer of these microsomal enzymes (den Tonkelaar and van Esch, 1974). Although HCB has a low acute toxicity for most species (>1,000 mg/kg), it has a wide range of biological effects at prolonged moderate exposure.

Subacute toxic effects of HCB were examined in rats after feeding with HCB for 15 weeks. Histopathological changes were confined to the liver and spleen. In the liver, there was an increase in the severity of centrilobular liver lesions with as little as 2 mg HCB/kg/day in the food. In contrast to the results of others, females were more susceptible to HCB than male rats. It would appear that 0.5 mg HCB/kg of body weight per day is the no-effect level in the rat (Kuiper-Goodman, et al. 1977). Unlike in the rat, it was not possible to induce porphyria in dogs with HCB (Gralla, et al. 1977). Swine are more susceptible to HCB in subacute studies than rats. Liver microsomal enzymes were induced in swine and excretion of coproporphyrin was increased by 0.5 mg HCB/kg/day after 13 and 8 weeks, respectively. It would appear that 0.05 mg HCB/kg/day in the diet is the "no-effect" level for swine (den Tonkelaar, et al. 1978).

In rats given 50 mg HCB/kg every other day for 53 weeks, an equilibrium between intake and elimination was achieved after nine weeks. In general, the changes observed in the long term studies resembled those described for short term studies. When the administration of HCB was discontinued, elimination of the xenobiotic continued slowly for many months (Koss, et al. 1978).

HCB caused a serious outbreak of hepatic porphyria in Turkey involving cutanea tarda lesions and porphyrinuria (Cam and Nigogosyan, 1963). This has been confirmed in a number of laboratory animals including rats (San Martin de Viale, et al. 1976), rabbits (Ivanov, et al. 1976), Japanese quail (Vos, et al. 1971), guinea pigs (Strik, 1973), swine (den Tonkelaar, et al. 1978), mice (Strik, 1973) and Rhesus monkeys (Iatropoulos, et al. 1976). Rats given 50 mg HCB/kg orally for 30 days showed enlarged livers, elevated liver porphyrin and elevated urine porphyrin (Carlson, 1977). In both rabbits and rats, HCB produced an increase in the excretion of uroporphyrin and coproporphyrin. The mechanism of action of HCB is not known, but it elicits an increase in δ-aminolevulinic acid synthetase, which is the rate-limiting enzyme in the biosynthesis of porphyrins (Timme, et al. 1974). The development of HCB-induced porphyria is accompanied by a progressive fall in hepatic uroporphyrinogen decarboxylase activity.

This change may be causally related to the disease (Elder, et al. 1976). The mitochondrial membrane may also be a factor in limiting the rate of porphyrin biosynthesis since some critical enzymes are intramitochondrial and others are cytoplasmic. It has been proposed that HCB may damage the mitochondrial membrane, thereby facilitating the flow of porphyrin intermediates through it (Simon, et al. 1976). Consistent with this proposal is the observation that HCB causes marked enlargement of rat hepatocytes, proliferation of smooth endoplasmic reticulum, formation of eosinophilic bodies, generation of large lipid vesicles, and mitochondrial swelling (Mollenhauer, et al. 1975).

It should be noted that the principal metabolite of HCB, pentachlorophenol, is not porphyrinogenic in the rat, so the formation of this metabolite is unlikely to play a role in HCB-induced porphyria (Lui, et al. 1976). Nevertheless, it is conceivable that other metabolites of HCB, particularly as a result of microsomal enzyme induction, might be the actual porphyrogenic agent (Lissner, et al. 1975).

An epidemic of HCB-induced cutanea tarda porphyria occurred in Turkey during the period 1955 to 1959 (Cam and Nigogosyan, 1963). More than 600 patients were observed during a 5-year period, and it was estimated that a total of 3,000 people were affected. The outbreak was traced to the consumption of wheat as food after it had been prepared for planting by treatment with hexachlorobenzene. The syndrome involves blistering and epidermolysis of the exposed parts of the body, particularly the face and hands. It was estimated that the subjects ingested 50 to 200 mg HCB/day for a relatively long period before the skin manifestations became apparent. The symptoms were seen mostly during the summer months, having been exacerbated by intense sunlight. The disease subsided and symptoms disappeared 20 to 30 days after discontinuation of intake of HCB-contaminated bread. Relapses were often seen, either because the subjects were eating HCB-containing wheat again, or because of redistribution of HCB stored in body fat.

A disorder called pembe yara was described in infants of Turkish mothers who either had HCB-induced porphyria or had eaten HCB-contaminated bread (Cam, 1960). The maternal milk contained HCB. At least 95 percent of these infants died within a year and in many villages, there were no children left between the ages of two and five during the period 1955-1960. With human tissue levels of HCB increasing measurably throughout the world, the effect of low chronic doses of this pesticide must be considered. HCB is stored in the body fat and transmitted through maternal milk. It is not known whether HCB is responsible for genetic damage to the progeny (Peters, 1976).

There was no evidence of cutaneous porphyria in 86 Louisiana residents having an average plasma HCB level of 3.6 µg/kg, with a maximum level of 345 µg HCB/kg. There was a possible correlation between plasma HCB levels and urinary coproporphyrin excretion or plasma lactate dehydrogenase activity but none with urinary uroporphyrin excretion (Burns and Miller, 1975). It should be noted that the people in Turkey showing symptoms of porphyria had ingested 1 to 4 mg HCB/kg/day for a relatively long period (Cam and Nigogosyan, 1963). It is speculated that some of the Louisiana workers had taken in several mg HCB per kg of body weight per day, at least sporadically.

Synergism and/or Antagonism

HCB at doses far below those causing mortality enhances the capability of animals to metabolize foreign organic compounds (see Metabolism section). This type of interaction may be of importance in determining the effects of other concurrently encountered xenobiotics on the animal (Carlson and Tardiff, 1976). An increase in paraoxon dealkylation activity was a more sensitive indicator of induction of microsomal enzyme activity in a liver fraction from rats fed a diet containing 2 mg HCB/kg for two weeks than cytochrome P-450 content or N-demethylase activity (Iverson, 1976).

HCB elicits significant and rather selective changes in lindane metabolism in rats (Chadwick, et al. 1977). Rats administered 7.5 mg HCB/kg/day orally for seven days had increased capability to metabolize and eliminate 1,2,3,4,5,6-hexachlorocyclohexane (lindane). As noted before, HCB caused liver enlargement and enhanced EPN metabolism. Rats fed HCB also had significantly increased ability to metabolize p-nitroanisole, but not methyl orange. HCB-treated rats excreted 35 percent of the administered lindane in their feces and 13.7 percent in their urine within 24 hours, in contrast to 12.7 percent in feces and 5.0 percent in urine of unexposed rats. The amount of lindane in fat and liver, 24 hours after administering 12.5 mg of lindane/kg orally, was less in HCB-treated rats than in unexposed controls (117 versus 60.7 mg/kg in fat and 9.57 versus 5.24 mg/kg in liver). The lindane content of the kidney was not significantly reduced (6.91 versus 5.94 mg/kg for HCB-treated versus unexposed rats). Rats pretreated with HCB excreted a significantly higher proportion of free chlorophenols, with a corresponding decrease in polar metabolites as compared to unexposed rats.

Prior exposure to HCB may alter the response of an animal to any of a variety of challenges. Mice fed a diet containing 167 mg HCB/kg have altered susceptibility to Salmonella typhosa 0901 lipopolysaccharide (endotoxin). The LD_{50} for exposed mice was about 40 mg endotoxin/kg, for mice fed HCB for three weeks 7.4 mg/kg, and for mice fed HCB for six weeks, 1.4 mg/kg. Mice fed HCB were also somewhat more susceptible to the malaria parasite Plasmodium than unexposed mice (Loose, et al. 1978).

Teratogenicity

The effect of HCB on reproduction has received limited attention. Dietary HCB adversely affected reproduction in the rat by decreasing the number of litters whelped and the number of pups surviving to weaning (Grant, et al. 1977). The fertility (numbers of litters whelped/number of females exposed to mating) of rats fed a diet containing 320 mg HCB/kg was decreased. This concentration of HCB in the food led to cumulative toxicity resulting in convulsions and death in some of the animals. The proportion of pups surviving five days was reduced when the parents had been fed a diet containing 160 mg HCB/kg and when the rats had been fed a diet of 80 mg HCB/kg for three generations. Birth weights were reduced in rats fed a diet containing 320 mg HCB/kg and in rats fed a diet containing 160 mg HCB/kg for two generations. The weights of 5-day-old pups were markedly less when the parents had been fed a diet containing 80 mg HCB/kg. The tissue of 21-day-old pups whose dam had been fed graded dietary levels of HCB contained progressively more drug. For example, the level of HCB in body fat was about 250 mg/kg when the dietary level was 10 mg/kg; 500 mg/kg in fat for 20 mg/kg in diet; 800 mg/kg in fat for 40 mg/kg in diet; 1,900 mg/kg in fat for 80 mg/kg in diet; and 2,700 mg/kg in fat for 160 mg/kg in diet. The highest HCB levels were in the body fat; for pups whose dam had been fed a diet containing 10 mg HCB/kg, the body fat contained 250 mg HCB/kg; liver, 9 mg/kg; kidney and brain, 4 mg/kg; and plasma, 1.3 mg/kg. HCB crossed the placenta of rats and accumulated in the fetus in a dose-related manner. HCB fed to pregnant mice and rats was deposited in the tissues in a dose-related manner. The HCB content of placentas was greater than that of the corresponding fetuses in both rats and mice, and equivalent to that in the yolk sac. The fetuses and placentas of rats had proportionally greater deposition of HCB than those of mice at the same dose levels. Upon multiple dosing, the deposition of HCB increased in both fetuses and placentas (Andrews and Courtney, 1976). HCB does not appear to be teratogenic for the rat even though the chemical is reaching the fetus (Khera, 1974).

Pregnant CD-1 mice given 50 mg HCB/kg/day orally on gestational days 7 to 11 showed essentially the same tissue distribution of drug on day 12 as similarly-treated, nonpregnant female mice. The HCB levels (mg/kg) were as follows: fat, about 500; thymus and skin, about 200; skeletal muscle, about 100; liver and brain, about 25; and spleen, kidney, uterus, and ovaries, about 12. The fetus contained 1.2 mg HCB/kg and the placenta 1.6 mg/kg. CD-1 mice administered 100 mg HCB/kg/day orally on gestational days 7 to 16 had increased maternal liver weight to body weight ratios and decreased fetal body weights. In addition, there was a small increase in the incidence of abnormal fetuses per litter. These abnormalities included cleft palate, small kidneys, club foot, and enlarged renal pelvis in both unexposed and exposed groups (Courtney, et al. 1976).

Mutagenicity

The capability of HCB to induce dominant lethal mutations in rats was tested after administering up to 60 mg HCB/kg/day orally for 10 days. There were no significant differences between the exposed and unexposed groups with respect to the incidence of pregnancies, corpora lutea, liver implants, or deciduomas (Khera, 1974).

HCB injected intraperitoneally into rats at 10 mg/kg elicited a marked induction of the hepatic cytochrome P-450 system. This liver microsomal fraction mediated the metabolic activation of 2,4-diaminoanisole to a mutagen (as measured by the Ames test) (Dybing and Aune, 1977). The mutagenic activities of several aromatic and polycyclic hydrocarbons are not associated with the parent compound but with metabolically activated products that react covalently with nucleic acid. As noted previously, HCB stimulates the hepatic cytochrome P-450 system and, thereby, has the potential to enhance the mutagenicity of other chemicals.

Carcinogenicity

Two studies have been conducted which indicate that HCB is a carcinogen. The carcinogenic activity of HCB in hamsters fed 4, 8, or 16 mg/kg/day for life was assessed (Cabral, et al. 1977). HCB appears to have multipotential carcinogenic activity; the incidence of hepatomas, haemangioendotheliomas, and thyroid adenomas was significantly increased. Whereas 10 percent of the unexposed hamsters developed tumors, 92 percent of the hamsters fed 16 mg HCB/kg/ day developed tumors. The incidence of tumor-bearing animals was dose-related: 56 percent for hamsters fed 4 mg HCB/kg/ day and 75 percent for 8 mg/kg/day. Thyroid tumors, hepatomas or liver haemangioendotheliomas were not detected in the unexposed group. An intake of 4 to 16 mg HCB/kg/day in hamsters is near the exposure range estimated for Turkish people who accidentally consumed HCB-contaminated grain (Cabral, et al. 1977).

The carcinogenic activity of HCB in mice fed 6.5, 13, or 26 mg/kg/day for life was assessed. The incidence of hepatomas was increased significantly in mice fed 13 or 26 mg HCB/kg/ day. None of the hepatomas occurred or metastasized in the untreated control groups. The results presented in the abstract of Cabral, et al. (1978) confirm their earlier conclusion that HCB is carcinogenic. However, the incidence of lung tumors in strain A mice treated three times a week for a total of 24 injections of 40 mg/kg each was not significantly greater than the incidence in control mice (Theiss, et al. 1977). Moreover, HCB did not induce hepatocellular carcinomas in ICR mice fed HCB at 1.5 or 7 mg/kg/day for 24 weeks (Shirai, et al. 1978).

CRITERION FORMULATION

Existing Guidelines and Standards

As far as can be determined, the Occupational Safety and Health Administration (OSHA) has not set a standard for occupational exposure of HCB. HCB has been approved for use as a pre-emergence fungicide applied to seed grain. The Federal Republic of Germany no longer allows the application of HCB-containing pesticides (Geike and Parasher, 1976). The government of Turkey discontinued the use of HCB-treated seed wheat in 1959 after its link to acquired toxic porphyria cutanea tarda was reported (Cam, 1959). Commercial production of HCB in the United Staes was discontinued in 1976 (Chem. Econ. Hdbk., 1977). The Louisiana State Department of Agriculture has set the tolerated level of HCB in meat fat at 0.3 mg/kg (U.S. EPA, 1976). The NHMRC (Australia) has used this same value for the tolerated level of HCB in cows' milk (Miller and Fox, 1973). WHO has set the tolerated level of HCB in cows' milk at 20 µg/kg in whole milk (Bakken and Seip, 1976). The New South Wales Department of Health (Australia) has recommended that the concentration of HCB in eggs must not exceed 0.1 mg/kg (Siyali, 1973). The value of 0.6 µg HCB/kg/day was suggested by FAO/WHO in 1974 as a reasonable upper limit for HCB residues in food for human consumption (FAO/WHO, 1974). The FAO/WHO recommendations for residues in foodstuffs were 0.5 mg/kg in fat for milk and eggs, and 1 mg/kg in fat for meat and poultry. Russia and Yugoslavia have set the maximum tolerated level of HCB in air at 0.9 mg/m^3 (Int. Labor Off. 1977).

Current Levels of Exposure

HCB appears to be distributed worldwide, with high levels of contamination found in agricultural areas devoted to wheat and related cereal grains and in industrial areas. HCB is manufactured and formulated for application to seed wheat to prevent bunt; however, most of the HCB in the environment comes from industrial processes. HCB is used as a starting material for the production of pentachlorophenol which is marketed as a wood preservative. HCB is one of the main substances in the tarry residue which results from the production of chlorinated hydrocarbons. HCB is formed as a by-product in the production of chlorine gas by the electrolysis of sodium chloride using a mercury electrode (Gilbertson and Reynolds, 1972).

People in the United States are exposed to HCB in air, water and food. HCB is disseminated in the air as dust particles and as a result of volatilization from sites having a high HCB-concentration. Airborne HCB-laden dust particles appear to have been a major cause of increased blood concentrations of HCB in the general public living near an industrial site in Louisiana (Burns and Miller, 1975). HCB is found in river water near industrial sites in quantities of as high as 2 µg/kg (Laska, et al. 1976) and even in finished drinking water at 5 ng/kg (U.S. EPA, 1975). HCB occurs in a wide variety of foods, in particular, terrestrial animal products, including dairy products and eggs (U.S. EPA, 1976). The dietary intake of HCB has been estimated to be 0.5 µg/day in Japan (Ushio and Doguchi, 1977) and 35 µg/day in Australia (Miller and

Fox, 1973). Breast-fed infants in Australia and Norway may consume 40 µg HCB/day (Miller and Fox, 1973; Bakken and Seip, 1976).

Table 2 lists HCB concentrations found in human adipose tissue collected throughout the world. The maximum HCB level reported was 22 mg/kg (Acker and Schulte, 1974).

The HCB content of human blood samples collected in Bavaria, Australia, and Louisiana is shown in Table 3. The maxium HCB concentration reported was 0.345 mg/kg in the sample from a Louisiana waste disposal worker (Burns and Miller, 1975).

The levels of HCB in body fat of swine and sheep were 6-fold and 8-fold greater, respectively than the dietary level (Hansen, et al. 1977). If these comparisons are valid when applied to man, it would appear that some adult humans have been exposed to several mg HCB/kg/day. A similar conclusion is reached by extrapolating the values for human blood. The HCB levels in blood of rats are about one tenth the dietary level (Kuiper-Goodman, et al. 1977).

Current evidence would indicate that food intake may be the primary source of the body burden of HCB for the general population although inhalation and dermal exposure may be more important in selected groups, e.g., industrial workers.

Special Groups at Risk

Several groups appear to be at increased risk. These include workers engaged directly in: (1) the manufacture of HCB or in processes in which HCB is a by-product, (2) the formulation of HCB-containing products, (3) the disposal of HCB-containing

TABLE 2

Hexachlorobenzene Content of Human Adipose Tissues at Autopsy

Source	No. Samples	Mean Values (mg/kg in Human Fat)	Reference
Australia	75	1.25	Brady and Siyali, 1972
"	81	1.31	Siyali, 1972
Papua and New Guinea	38	0.26	Brady and Siyali, 1972
Japan	241	0.08	Curley, et al. 1973
Canada	3	0.09	Mes and Campbell, 1976
"	16	0.025	Mes, et al. 1977
"	50	0.107	Mes, et al. 1977
"	57	0.060	Mes, et al. 1977
"	22	0.015	Mes, et al. 1977
"	27	0.043	Mes, et al. 1977
Germany	56	2.9	Acker and Schulte, 1974
"	54	8.2	Acker and Schulte, 1974
"	54	5.9	Acker and Schulte, 1974
"	59	4.8	Acker and Schulte, 1974
"	59	6.4	Acker and Schulte, 1974
"	93	4.8	Acker and Schultr, 1974

TABLE 3

The HCB Content of Human Blood Samples

Source	No. Samples	Mean Values (mg/kg in Blood)	Referemce
Bavaria	98 boys	0.022	Richter and Schmid, 1976
"	96 girls	0.017	Richter and Schmid, 1976
Australia	185 exposed	0.055	Siyali, 1972
"	52 unexposed	0.022	Siyali, 1972
"	76	0.058	Siyali and Ouw, 1973
Louisiana	86	0.0036	Burns and Miller, 1975

wastes; and (4) the application of HCB-containing products. Other groups at risk are the general public living near industrial sites, populations consuming large amounts of contaminated fish, pregnant women, fetuses, and breast-fed infants. Two lines of evidence indicate that infants may be at risk. It has been demonstrated that human milk contains HCB, and some infants may be exposed to relatively high concentrations of HCB from that source alone (Miller and Fox, 1973; Bakken and Seip, 1976). Moreover, some infants of Turkish mothers who consumed HCB-contaminated bread developed a fatal disorder called pembe yara. In some Turkish villages in the region most affected by HCB-poisoning, few infants survived during the period 1955-1960 (Cam, 1960).

Occupational exposure is associated with an increased body burden of HCB. Plant workers in Louisiana have about 200 µg HCB/kg in blood (Burns and Miller, 1975). The HCB content of body fat exceeded 1 mg/kg in many parts of the world where HCB contamination of the environment is extensive (Brady and Siyali, 1972; Acker and Schulte, 1974).

The massive episode of human poisoning resulting from the consumption of bread prepared from HCB-treated seed wheat brought to light the misuse of HCB-treated grain (Cam and Nigogosyan, 1963). In spite of warnings, regulations, and attempts at public education, HCB-treated grain apparently still finds its way into the food chain, for example, in fish food (Hansen, et al. 1976; Laska, et al. 1976). The difficulty in tracing the source of HCB contamination in a diet for laboratory animals emphasizes the difficulties encountered in tracing the source of HCB in foodstuffs for human consumption (Yang, et al. 1976).

As noted previously, adipose tissue acts as a reservoir for HCB. Depletion of fat depots can result in mobilization and redistribution of stored HCB. Weight loss for any reason may result in a dramatic redistribution of HCB contained in adipose tissue; if the stored levels of HCB are high, adverse effects might ensue. Many humans restrict their dietary intake voluntarily or because of illness. In these instances, the redistribution of the HCB body burden becomes a potential added health hazard (Villeneuve, 1975).

Basis and Derivation of Criterion

Among the studies reviewed by this document, only two appear suitable for use in the risk assessment: the mouse study of Cabral, et al. (1978) and the hamster study of Cabral, et al. 1977. These two studies are described in detail in Appendix I.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities". HCB is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of HCB in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be unfeasible in some cases, and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of HCB corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the table below:

Exposure Assumption (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 grams fish and shellfish. (2)	0.072 ng/l	0.72 ng/l	7.2 ng/l
Consumption of fish and shellfish only.	0.074 ng/l	0.74 ng/l	7.4 ng/l

(1) Calculated from the linearized multistage model described in the Human Health Methodology Appendices to the October 1980 Federal Register notice, which announced the availability of this document. Appropriate bioassay data used in the calculation of the model are presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly

proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Ninety-seven percent of the HCB exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 8,690-fold. The remaining 3 percent of HCB exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of HCB, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding HCB concentrations and (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding HCB concentrations. Because data indicating other sources of HCB exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

REFERENCES

Acker, L. and E. Schulte. 1971. Zum Vorkommen von Hexachlorbenzol und polychlorierten Biphenylen neben chlorierten Insektiziden in menschlichem Fettgewebe und in Humanmilch. Ernahrungsforschung. 16: 559. (Ger.)

Acker, L. and E. Schulte. 1974. Chlorkohlenwasserstoffe im menschlichen fett. Naturwissensch. 61: 32. (Ger.)

Albro, P.W. and R. Thomas. 1974. Intestinal absorption of hexachlorobenzene and hexachlorocyclohexane isomers in rats. Bull. Environ. Contam. Toxicol. 12: 289.

Andrews, J.E. and K.D. Courtney. 1976. Inter- and intralitter variation of hexachlorobenzene (HCB) deposition in fetuses. Toxicol. Appl. Pharmacol. 37: 128.

Bakken, A.F. and M. Seip. 1976. Insecticides in human breast milk. Act. Paediat. Scand. 65: 535.

Beall, M.L., Jr. 1976. Persistence of aerially applied HCB on grass and soil. Jour. Environ. Qual. 5: 367.

Beck, J. and K.E. Hansen. 1974. The degradation of quintozene, pentachlorobenzene, hexachlorobenzene, and pentachloroaniline in soil. Pestic. Sci. 5: 41.

Brady, M.N. and D.S. Siyali. 1972. Hexachlorobenzene in human body fat. Med. Jour. Australia. 1: 518.

Burns, J.E. and F.M. Miller. 1975. Hexachlorobenzene contamination: Its effects in a Louisiana population. Arch. Environ. Health. 30: 44.

Cabral, J.R.P., et al. 1977. Carcinogenic activity of hexachlorobenzene in hamsters. Nature. 269: 510.

Cabral, J.R.P., et al. 1978. Carcinogenesis study in mice with hexachlorobenzene. Toxicol. Appl. Pharmacol. 45: 323.

Cam, C. 1959. Cutaneous porphyria related to intoxication. Dirim. 34: 11. (Tur.)

Cam, C. 1960. Une nouvelle dermatose epidemique des enfants. Ann. Dermatol. Syphiligr. 87: 393. (Fre.)

Cam, C. and G. Nigogosyan. 1963. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. Jour. Am. Med. Assoc. 183: 88.

Carlson, G.P. 1977. Chlorinated benzene induction of hepatic porphyria. Experientia. 33: 1627.

Carlson, G.P. 1978. Induction of cytochrome P-450 by halogenated benzenes. Biochem. Pharmacol. 27: 361.

Carlson, G.P. and R.G. Tardiff. 1976. Effect of chlorinated benzenes on the metabolism of foreign organic compounds. Toxicol. Appl. Pharmacol. 36: 383.

Chadwick, R.W., et al. 1977. Comparative enzyme induction and lindane metabolism in rats pre-treated with various organochlorine pesticides. Xenobiotica. 7: 235.

Chemical Economic Handbook. 1977. Chlorobenzenes-Salient Statistics. In: Chemical Economic Handbook, Stanford Res. Inst. Int., Menlo Park, California.

Courtney, K.D., et al. 1976. The effects of pentachloronitrobenzene, hexachlorobenzene, and related compounds on fetal development. Toxicol. Appl. Pharmacol. 35: 239.

Cromartie, E., et al. 1975. Residues of organochlorine pesticides and polychlorinated biphenyls and autopsy data for bald eagles, 1971-72. Pestic. Monitor. Jour. 9: 11.

Curley, A., et al. 1973. Chlorinated hydrocarbon pesticides and related compounds in adipose tissue from people of Japan. Nature. 242: 338.

den Tonkelaar, E.M. and G.J. van Esch. 1974. No-effect levels of organochlorine pesticides based on induction of microsomal liver enzymes in short-term toxicity experiments. Toxicology. 2: 371.

den Tonkelaar, E.M., et al. 1978. Hexachlorobenzene toxicity in pigs. Toxicol. Appl. Pharmacol. 43: 137.

Dybing, E. and T. Aune. 1977. Hexachlorobenzene induction of 2,4-diaminoanisole mutagenicity *in vitro*. Acta Pharmacol. Toxicol. 40: 575.

Elder, G.H., et al. 1976. The effect of the porphyrogenic compound, hexachlorobenzene, on the activity of hepatic uroporphyrinogen decarboxylase in the rat. Clin. Sci. Mol. Med. 51: 71.

Engst, R., et al. 1976. The metabolism of hexachlorobenzene (HCB) in rats. Bull. Environ. Contam. Toxicol. 16: 248.

Food and Agriculture Organization. 1974. 1973 evaluations of some pesticide residues in food. FAO/AGP/1973/M/9/1; WHO Pestic. Residue Ser. 3. World Health Org., Rome, Italy. p. 291.

Freitag, D., et al. 1974. Ecological Chemistry. LXXVI: Fate of HCB-^{14}C in summer wheat and soil after seed treatment. Chemosphere. 3: 139.

Geike, F. and C.D. Parasher. 1976. Effect of hexachlorobenzene (HCB) on some growth parameters of *Chlorella pyrenoidosa*. Bull. Environ. Contam. Toxicol. 15: 670.

Gilbertson, M. and L.M. Reynolds. 1972. Hexachlorobenzene (HCB) in the eggs of common terns in Hamilton Harbour, Ontario. Bull. Environ. Contam. Toxicol. 7: 371.

Gralla, E.J., et al. 1977. Toxic effects of hexachlorobenzene after daily administration to beagle dogs for one year. Toxicol. Appl. Pharmacol. 40: 227.

Grant, D.L., et al. 1977. Effect of hexachlorobenzene on reproduction in the rat. Arch. Environ. Contam. Toxicol. 5: 207.

Hansen, L.G., et al. 1976. Effects of dietary Aroclor 1242 on channel catfish, *Ictalurus punctatus*, and the selective accumulation of PCB components. Jour. Fish Res. Board of Canada. 33: 1343.

Hansen, L.G., et al. 1977. Effects and residues of dietary hexachlorobenzene in growing swine. Jour. Toxicol. Environ. Health. 2: 557.

Iatropoulos, M.J., et al. 1975. Absorption, transport and organotropism of dichlorobiphenyl (DCB), dieldrin, and hexachlorobenzene (HCB) in rats. Environ. Res. 10: 384.

Iatropoulos, M.J., et al. 1976. Morphological effects of hexachlorobenzene toxicity in female Rhesus monkeys. Toxicol. Appl. Pharmacol. 37: 433.

International Labor Office. 1977. Occupational Exposure Levels for Airborne Substances. In: Occupational Health Series No. 37. International Labor Office, Geneva.

Isensee, A.R., et al. 1976. Soil persistence and aquatic bioaccumulation potential of hexachlorobenzene (HCB). Jour. Agric. Food. Chem. 24: 1210.

Ivanov, E., et al. 1976. Studies on the mechanism of the changes in serum and liver γ-glutamyl transpeptidase activity. Enzyme. 21: 8.

Iverson, F. 1976. Induction of paraoxon dealkylation by hexachlorobenzene (HCB) and Mirex. Jour. Agric. Food. Chem. 24: 1238.

Johnson, J.L., et al. 1974. Hexachlorobenzene (HCB) residues in fish. Bull. Environ. Contam. Toxicol. 11: 393.

Kan, C.A. and L.G.M.T. Tuinstra. 1976. Accumulation and excretion of certain organochlorine insecticides in broiler breeder hens. Jour. Agric. Food. Chem. 24: 775.

Khera, K.S. 1974. Teratogenicity and dominant lethal studies on hexachlorobenzene in rats. Food Cosmet. Toxicol. 12: 471.

Koeman, J.H., ed. 1972. Side-effects of persistent pesticides and other chemicals on birds and mammals in the Netherlands. TNO-Nieuws.

Kohli, J., et al. 1976. The metabolism of higher chlorinated benzene isomers. Can. Jour. Biochem. 54: 203.

Koss, G. and W. Koransky. 1975. Studies on the toxicology of hexachlorobenzene. I. Pharmacokinetics. Arch. Toxicol. 34: 203.

Koss, G. and D. Manz. 1976. Residues of hexachlorobenzene in wild mammals of Germany. Bull. Environ. Contam. Toxicol. 15: 189.

Koss, G., et al. 1976. Studies on the toxicology of hexachlorobenzene. II. Identification and determination of metabolites. Arch. Toxicol. 35: 107.

Koss, G., et al. 1978. Studies on the toxicology of hexachlorobenzene. III. Observations in a long-term experiment. Arch. Toxicol. 40: 285.

Kuiper-Goodman, T., et al. 1977. Subacute toxicity of hexachlorobenzene in the rat. Toxicol. Appl. Pharmacol. 40: 529.

Laseter, J.L., et al. 1976. An ecological study of hexachlorobenzene (HCB). EPA 560-6-76-009, U.S. Environ. Prot. Agency, Washington, D.C.

Laska, A.L., et al. 1976. Distribution of hexachlorobenzene and hexachlorobutadiene in water, soil, and selected aquatic organisms along the lower Mississippi River, Louisiana. Bull. Environ. Contam. Toxicol. 15: 535.

Leoni, V. and S.U. D'Arca. 1976. Experimental data and critical review of the occurrence of hexachlorobenzene in the Italian environment. Sci. Total. Environ. 5: 253.

Lissner, R., et al. 1975. Hexachlorobenzene induced porphyria in rats. Relationship between porphyrin excretion and induction of drug metabolizing liver enzymes. Biochem. Pharmacol. 24: 1729.

Loose, L.D., et al. 1978. Impaired host resistance to endotoxin and malaria in polychlorinated bipheynl and hexachlorobenzene-treated mice. Infect. Immun. 20: 30.

Lu, P.Y. and R.L. Metcalf. 1975. Environmental fate and biodegradability of benzene derivatives as studied in a model aquatic ecosystem. Environ. Health Perspect. 10: 269.

Lui, H., et al. 1976. Hexachlorobenzene Porphyria. In: Porphyrins in Human Diseases. Karger, Basel. p. 405.

Mes, J. and D.S. Campbell. 1976. Extraction efficiency of polychlorinated biophenyl, organochlorine pesticides and phthalate esters from human adipose tissue. Bull. Environ. Contam. Toxicol. 16: 53.

Mes, J., et al. 1977. Polychlorinated biphenyl and organochloride pesticide residues in adipose tissue of Canadians. Bull. Environ. Contam. Toxicol. 17: 196.

Miller, G.J. and J.A. Fox. 1973. Chlorinated hydrocarbon pesticide residues in Queensland human milks. Med. Jour. Australia. 2: 261.

Mollenhauer, H.H., et al. 1975. Ultrastructural changes in liver of the rat fed hexachlorobenzene. Am. Jour. Vet. Res. 36: 1777.

Morita, M. and S. Oishi. 1975. Clearance and tissue distribution of hexachlorobenzene in rats. Bull. Environ. Contam. Toxicol. 14: 313.

Mumma, C.E. and E.W. Lawless. 1975. "Task I - Hexachlorobenzene and hexachlorobutadiene pollution from chlorocarbon processes". EPA 530-3-75-003, U.S. Environ. Prot. Agency, Washington, D.C.

National Academy of Sciences. 1975. Assessing potential ocean pollutants. Washington, D.C. p. 188.

Parke, D.V. and R.T. Williams. 1960. Studies in detoxication. Biochem. Jour. 74: 5.

Peters, H.A. 1976. Hexachlorobenzene poisoning in Turkey. Fed. Proc. 35: 2400.

Plimmer, J.R. and U.I. Klingebiel. 1976. Photolysis of hexachlorobenzene. Jour. Agric. Food Chem. 24: 721.

Richter, E. and A. Schmid. 1976. Hexachlorobenzolgehalt im Vollblut von Kindern. Arch. Toxicol. 3[illegible]: 141. (Ger.)

Rourke, D.R., et al. 1977. Identification of hexachlorobenzene as a contaminant in laboratory plastic wash bottles. Jour. AOAC. 60: 233.

Sanborn, J.R., et al. 1977. Uptake and elimination of [^{14}C] hexachlorobenzene (HCB) by the green sunfish Lepomis cyanellus Raf., after feeding contaminated food. Jour. Agric. Food Chem. 25: 551.

San Martin de Viale, L.C., et al. 1976. Experimental Porphyria Induced in Rats by Hexachlorobenzene. In: Porphyrins in Human Diseases. Karger, Basel. p. 453.

Savage, E.P. 1976. National study to determine levels of chlorinated hydrocarbon insecticides in human milk. EPA Contract No. 68-01-3190. Off. Tox. Subst. Washington, D.C.

Schaefer, R.E., et al. 1976. Residues of chlorinated hydrocarbons in North Sea animals in relation to biological parameters. Ber. At. Wiss. Komm. Merrlsforsch. 24: 225.

Shirai, T., et al. 1978. Hepatocarcinogenicity of polychlorinated terphenyl (PCT) in ICR mice and its enhancement by hexachlorobenzene (HCB). Cancer Lett. 4: 271.

Simon, N., et al. 1976. The Role of Damages in Cellular Membrane Structures in the Development of Porphyria Cutanea Tarda. In: Porphyrins in Human Diseases. Karger, Basel. p. 423.

Simpson, G.R. and A. Shandar. 1972. Exposure to chlorinated hydrocarbon pesticides by pest control operators. Med. Jour. Australia. 2: 1060.

Sims, G.G., et al. 1977. Organochlorine residues in fish and fishery products from the Northwest Atlantic. Bull. Environ. Contam. Toxicol. 18: 697.

Siyali, D.S. 1972. Hexachlorobenzene and other organochlorine pesticides in human blood. Med. Jour. Australia. 2: 1063.

Siyali, D.S. 1973. Polychlorinated biphenyls, hexachlorobenzene and other organochlorine pesticides in human milk. Med. Jour. Australia. 2: 815.

Siyali, D.S. and K.H. Ouw. 1973. Chlorinated hydrocarbon pesticides in human blood - Wee Waa survey. Med. Jour. Australia. 2: 908.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stonard, M.D. 1975. Mixed type hepatic microsomal enzyme induction by hexachlorobenzene. Biochem. Pharmacol. 24: 1959.

Stonard, M.D. and J.B. Greig. 1976. Different patterns of hepatic microsomal enzyme activity produced by administration of pure hexachlorobiphenyl isomers and hexachlorobenzene. Chem. Biol. Interact. 15: 365.

Strik, J.J.T.W.A. 1973. Species differences in experimental porphyria caused by polyhalogenated aromatic compounds. Enzyme. 16: 224.

Sundlof, S.F., et al. 1976. Pharmacokinetics of hexachlorobenzene in male laboratory beagles. Pharmacologist. 18: 149.

Theiss, J.C., et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37: 2717.

Timme, A.H., et al. 1974. Symptomatic porphyria. Part II. Hepatic changes with hexachlorobenzene. S. African Med. Jour. 48: 1833.

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Report to Congress. EPA 560/4-75- 003. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. EPA. 1976. Environmental contamination from hexachlorobenzene. EPA 560/6-76-014. Off. Tox. Subst. 1-27.

U.S. EPA. 1980a. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, Calif. Final rep., Task II, Contract No. 68-01-3887.

U.S. EPA. 1980b. Laboratory data. Environ. Res. Lab. Duluth, Minnesota. (Unpub.)

Ushio, F. and M. Doguchi. 1977. Dietary intakes of some chlorinated hydrocarbons and heavy metals estimated on the experimentally prepared diets. Bull. Environ. Contam. Toxicol. 17: 707.

Veith, G.D., et al. 1977. Residues of PCBs and DDT in the western Lake Superior ecosystem. Arch. Environ. Contam. Toxicol. 5: 487.

Veith, G.D., 1980. Memorandum to C.E. Stephan. U.S. EPA. April 14.

Villeneuve, D.C. 1975. The effect of food restriction on the redistribution of hexachlorobenzene in the rat. Toxicol. Appl. Pharmacol. 31: 313.

Villeneuve, D.C. and W.H. Newsome. 1975. Toxicity and tissue levels in the rat and guinea pig following acute hexachlorobenzene administration. Bull. Environ. Contam. Toxicol. 14: 297.

Vos, J.G., et al. 1971. Toxicity of hexachlorobenzene in Japanese quail with special reference to porphyria, liver damage, reproduction, and tissue residues. Toxicol. Appl. Pharmacol. 18: 944.

White, D.E. and T.E. Kaiser. 1976. Residues of organochlorines and heavy metals in ruddy ducks from Delaware River, 1973. Pestic. Monitor. Jour. 9: 155.

Wilson, D.W. and L.G. Hansen. 1976. Pharmacokinetics of hexachlorobenzene in growing swine. Pharmacologist. 18: 196.

Yang, R.S.H., et al. 1976. Hexachlorobenzene contamination in laboratory monkey chow. Jour. Agric. Food Chem. 24: 563.

Zitko, V. 1976. Levels of chlorinated hydrocarbons in eggs of double-crested cormorants from 1971 to 1975. Bull. Environ. Contam. Toxicol. 16: 399.

Zitko, V. and O. Hutzinger. 1976. Uptake of chloro- and bromobiphenyls, hexachloro- and hexabromobenzene by fish. Bull. Environ. Contam. Toxicol. 16: 665.

SUMMARY-CRITERION FORMULATION

Existing Guidelines and Standards

Monochlorobenzene

The Threshold Limit Value (TLV) for MCB as adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) (1971) is 75 ppm (350 mg/m^3). The American Industrial Hygiene Association Guide (1964) considered 75 ppm to be too high. The recommended maximal allowable concentrations in air in other countries are: Soviet Union, 10 ppm; Czechoslovakia, 43 ppm; and Romania, 0.05 mg/l. The latter value for Romania was reported by Gabor and Raucher (1960) and is equivalent to 10 ppm.

Trichlorobenzene

A proposed ACGIH Threshold Limit Value (TLV) standard for TCBs is 5 ppm (40 mg/m^3) as a ceiling value (ACGIH, 1977). Sax (1975) recommends a maximum allowable concentration of 50 ppm in air for commercial TCB, a mixture of isomers. Coate, et al. (1977), citing their studies, recommends that the TLV should be set below 25 ppm, preferably at 5 ppm (40 mg/m^3). Gurfein and Parlova (1962) indicate that in the Soviet Union the maximum allowable concentration for TCB in water is 30 µg/l which is intended to prevent organoleptic effects.

Tetrachlorobenzene

The maximal permissible concentration of TeCB in water established by the Soviet Union is 0.02 mg/l (U.S. EPA, 1977).

Pentachlorobenzene

No guidelines or standards for pentacnlorobenzene could be located in the available literature.

Hexachlorobenzene

As far as can be determined, the Occupational Safety and Health Administration has not set a standard for occupational exposure to HCB. HCB has been approved for use as a pre-emergence fungicide applied to seed grain. The Federal Republic of Germany no longer allows the application of HCB-containing pesticides (Geike and Parasher, 1976). The government of Turkey discontinued the use of HCB-treated seed wheat in 1959 after its link to acquired toxic porphyria cutanea tarda was reported (Cam, 1959). Commercial production of HCB in the United States was discontinued in 1976 (Chem. Econ. Hdbk., 1977). The Louisiana State Department of Agriculture has set the tolerated level of HCB in meat fat at 0.3 mg/kg (U.S. EPA, 1976). The NHMRC (Australia) has used this same value for the tolerated level of HCB in cows' milk (Miller and Fox, 1973). WHO has set the tolerated level of HCB in cows' milk at 20 μg/kg in whole milk (Bakken and Seip, 1976). The New South Wales Department of Health (Australia) has recommended that the concentration of HCB in eggs must not exceed 0.1 mg/kg (Siyali, 1973). The value of 0.6 μg HCB/kg/day was suggested by FAO/WHO in 1974 as a reasonable upper limit for HCB residues in food for human consumption (FAO/WHO, 1974). The FAO/WHO recommendations for residues in foodstuffs were 0.5 mg/kg in fat for milk and eggs, and 1 mg/kg in fat for meat and poultry. Russia and Yugoslavia have set the maximum tolerated level of HCB in air at 0.9 mg/m^3 (Int. Labor Off., 1977).

Current Levels of Exposure

Monochlorobenzene

MCB has been detected in water monitoring surveys of various U.S. cities (U.S. EPA, 1975; 1977) as was presented in the text in Table 1. Levels reported were: ground water - 1.0 µg/l; raw water contaminated by various discharges - 0.1 to 5.6 µg/l; upland water - 4.7 µg/l; industrial discharge - 8.0 to 17.0 µg/l and municipal water - 27 µg/l. These data show a gross estimate of possible human exposure to MCB through the water route.

Evidence of possible exposure from food ingestion is indirect. MCB is stable in water and thus could be bioaccumulated by edible fish species.

The only data concerning exposure to MCB via air are from the industrial working environment. Reported industrial exposures to MCB are 0.02 mg/l (average value) and 0.3 mg/l (highest value) (Gabor and Raucher, 1960); 0.001 to 0.01 mg/l (Levina, et al. 1966); and 0.004 to 0.01 mg/l (Stepanyen, 1966).

Trichlorobenzene

Possible human exposure to TCBs might occur from municipal and industrial wastewater and from surface runoff (U.S. EPA, 1977). Municipal and industrial discharges contained from 0.1 µg/l to 500 µg/l. Suface runoff has been found to contain 0.006 to 0.007 µg/l.

In the National Organics Reconaissance Survey (NORS) conducted by EPA in 1975, trichlorobenzene was found in drinking water at a level of 1.0 µg/l.

Tetrachlorobenzene

No data are available on current levels of exposure. However, the report by Morita, et al. (1975) gives some indication of exposure. Morita, et al. (1975) examined adipose tissue samples obtained at general hospitals and medical examiners' offices in central Tokyo. Samples from 15 individuals were examined; this represented 5 males and 10 females between the ages of 13 and 78. The tissues were examined for 1,2,4,5-TeCB as well as for 1,4-dichlorobenzene and hexachlorobenzene. The TeCB content of the fat ranged from 0.006 to 0.039 mg/kg of tissue; the mean was 0.019 mg/kg. The mean concentrations of 1,4-dichlorobenzene and hexachlorobenzene were 1.7 mg/kg and 0.21 mg/kg, respectively. Neither age nor sex correlated with the level of any of the chlorinated hydrocarbons in adipose tissue.

Pentachlorobenzene

Morita, et al. (1975) examined levels of QCB in adipose tissue samples obtained from general hospitals and medical examiners' offices in central Tokyo. The samples were collected from a total of 15 people. By gas chromatography, the authors found the residual level of QCB range from 0.004 μg/g to 0.020 μg/g, with a mean value of 0.09 μg/g of fat. Lunde and Bjorseth (1977) examined blood samples from workers with occupational exposure to pentachlorobenzene and found that their blood samples contained higher levels of this compound than a comparable group of workers not exposed to chlorobenzenes.

Hexachlorobenzene

HCB appears to be distributed worldwide, with high levels of contamination found in agricultural areas devoted to wheat and related cereal grains and in industrial areas. HCB is manufactured and formulated for application to seed wheat to prevent bunt; however, most of the HCB in the environment comes from industrial processes. HCB is used as a starting material for the production of pentachlorophenol which is marketed as a wood preservative. HCB is one of the main substances in the tarry residue which results from the production of chlorinated hydrocarbons. HCB is formed as a by-product in the production of chlorine gas by the electrolysis of sodium chloride using a mercury electrode (Gilbertson and Reynolds, 1972).

People in the United States are exposed to HCB in air, water, and food. HCB is disseminated in the air as dust particles and as a result of volatilization from sites having a high HCB-concentration. Airborne HCB-laden dust particles appear to have been a major cause of increased blood concentrations of HCB in the general public living near an industrial site in Louisiana (Burns and Miller, 1975). HCB is found in river water near industrial sites in quantities of as high as 2 µg/kg (Laska, et al. 1976) and even in finished drinking water at 5 ng/kg (U.S. EPA, 1975). HCB occurs in a wide variety of foods, in particular, terrestrial animal products, including dairy products and eggs (U.S. EPA, 1976). The dietary intake of HCB has been estimated to be 0.5 µg/day in Japan (Ushio and Doguchi, 1977) and 35 µg/day in Australia (Miller and

Fox, 1973). Breast-fed infants in Australia and Norway may consume 40 µg HCB/day (Miller and Fox, 1973; Bakken and Seip, 1976). Table 1 lists HCB concentrations found in human adipose tissues collected throughout the world. The maximum HCB level reported was 22 mg/kg (Acker and Schulte, 1974). The HCB content of human blood samples is given in Table 2. The maximum HCB concentration reported was 0.345 mg/kg which was found in a sample from a Louisiana waste disposal worker.

The levels of HCB in body fat of swine and sheep were sixfold and eightfold greater, respectively, than the dietary level (Hansen, et al. 1977). If these comparisons are valid when applied to man, it would appear that some adult humans have been exposed to several mg HCB/kg/day. A similar conclusion is reached by extrapolating the values for human blood. The HCB levels in blood of rats are about one tenth less than the dietary level (Kuiper-Goodman, et al. 1977).

Current evidence would indicate that food intake may be the primary source of the body burden of HCB for the general population although inhalation and dermal exposure may be more important in selected groups, e.g., industrial workers.

Special Groups at Risk

Monochlorobenzene

The major group at risk of MCB intoxication are individuals exposed to MCB in the workplace. Girard, et al. (1969) reported the case of an elderly female exposed to a glue containing 0.07 percent MCB for a period of six years. She had symptoms of headache, irritation of the eyes and the upper respiratory tract, and

TABLE 1

Hexachlorobenzene Content of Human Adipose Tissues at Autopsy

Sourcee	No. Samples	Mean Values (mg/kg in Human Fat)	Reference
Australia	75	1.25	Brady and Siyali, 1972
"	81	1.31	Siyali, 1972
Papua and New Guinea	38	0.26	Brady and Siyali, 1972
Japan	241	0.08	Curley, et al. 1973
Canada	3	0.09	Mes and Campbell, 1976
"	16	0.025	Mes, et al. 1977
"	50	0.107	Mes, et al. 1977
"	57	0.060	Mes, et al. 1977
"	22	0.015	Mes, et al. 1977
"	27	0.043	Mes, et al. 1977
Germany	56	2.9	Acker and Schulte, 1974
"	54	8.2	Acker and Schulte, 1974
"	54	5.9	Acker and Schulte, 1974
"	59	4.8	Acker and Schulte, 1974
"	59	6.4	Acker and Schulte, 1974
"	93	4.8	Acker and Schultr, 1974

TABLE 2

The HCB Content of Human Blood Samples

Source	No. Samples	Mean Values (mg/kg in Blood)	Reference
Bavaria	98 boys	0.022	Richter and Schmid, 1976
"	96 girls	0.017	Richter and Schmid, 1976
Australia	185 exposed	0.055	Siyali, 1972
"	52 unexposed	0.022	Siyali, 1972
"	76	0.058	Siyali and Ouw, 1973
Louisiana	86	0.0036	Burns and Miller, 1975

was diagnosed to have medullary aplasia. Smirnova and Granik (1970) reported on three adults who developed numbness, loss of consciousness, and hyperemia of the conjunctiva and the pharynx following exposure to "high" levels of MCB. Information concerning the ultimate course of these individuals is not available. Gabor, et al. (1962) described toxic effects on individuals who were exposed to benzene, chlorobenzene, and vinyl chloride. Eighty-two workers examined for certain biochemical indices showed a decreased catalase activity in the blood and an increase in peroxidase, indophenol oxidase, and glutathione levels. Dunaeveskii (1972) reported on the occupational exposure of workers exposed to the chemicals involved in the manufacture of chlorobenzene at limits below the allowable levels. After more than three years, cardiovascular effects were noted as pain in the area of the heart, bradycardia, irregular variations in electrocardiogram, decreased contractile function of myocardium, and disorders in adaptation to physical loading. Filatova, et al. (1973) reported on the prolonged exposure of individuals involved in the production of diisocyanates to factory air which contained MCB as well as other chemicals. Diseases noted include asthmatic bronchitis, sinus arrhythmia, tachycardia, arterial dystrophy, and anemic tendencies. Petrova and Vishnevskii (1972) studied the course of pregnancy and deliveries in women exposed to air in a varnish manufacturing factory where the air contained three times the maximum permissible level of MCB but also included toluene, ethyl chloride, butanol, ethyl bromide, and orthosilisic acid ester.

The only reported significant adverse effect of this mixed exposure was toxemia during pregnancy.

Tetrachlorobenzene

The primary groups at risk from the exposure to TeCB are those who deal with it in the workplace. Since it is a metabolite of certain insecticides, it might be expected that certain individuals exposed to those agents might experience more exposure to TeCB, especially since its elimination rate might be relatively slow in man. Individuals consuming large quantities of fish may also be at risk due to the proven bioconcentration of TeCB in fish. The bioconcentration factor for 1,2,4,5-TeCB is 1,125.

Pentachlorobenzene

A group at increased risk would appear to be those individuals exposed occupationally. Due to the persistence of the compound in the food chain, an increase in the body burden of QCB might be expected in individuals on high fish diets or diets high in agricultural products containing QCB residues of PCNB sprays.

Hexachlorobenzene

Several groups appear to be at increased risk; these include workers engaged directly in: (1) the manufacture of HCB or in processes in which HCB is a byproduct; (2) the formulation of HCB-containing products; (3) the disposal of HCB-containing wastes; and (4) the application of HCB-containing products. They also include the general public living near industrial sites, pregnant women, fetuses, and breast-fed infants and populations consuming large amounts of contaminated fish. Two lines of evidence indicate that infants may be at risk. It has been demonstrated that human milk contains HCB, and some infants may be exposed to relatively high concentrations of HCB from that source alone (Miller and Fox, 1973; Bakken and Seip, 1976). Moreover, some infants of Turkish mothers who consumed HCB-contaminated bread developed a fatal disorder called pembe yara. In some Turkish villages in the region most affected by HCB-poisoning, few infants survived during the period 1955-1960 (Cam, 1960).

Occupational exposure is associated with an increased body burden of HCB. Plant workers in Louisiana have about 200 μg HCB/kg in blood (Burns and Miller, 1975). The HCB content of body fat exceeds 1 mg/kg in many parts of the world where HCB contamination of the environment is extensive (Brady and Siyali, 1972; Acker and Schulte, 1974).

The massive episode of human poisoning resulting from the consumption of bread prepared from HCB-treated seed wheat brought to light the misuse of HCB-treated grain (Cam and Nigogosyan, 1963). In spite of warnings, regulations, and attempts at public education, HCB-treated grain apparently still finds its way into the food chain, for example, in fish food (Hansen, et al. 1976; Laska, et al. 1976). The difficulty in tracing the source of HCB contamination in a diet for laboratory animals emphasizes the difficulties encountered in tracing the source of HCB in foodstuffs for human consumption (Yang, et al. 1976).

As noted previously, adipose tissue acts as a reservoir for HCB. Depletion of fat depots can result in mobilization and redistribution of stored HCB. Weight loss for any reason may result in a dramatic redistribution of HCB contained in adipose tissue;

if the stored levels of HCB are high, adverse effects might ensue. Many humans restrict their dietary intake voluntarily or because of illness. In these instances, the redistribution of the HCB body burden becomes a potential added health hazard (Villeneuve, 1975).

Basis and Derivation of Criteria

Monochlorobenzene

There is no information in the literature which indicates that monochlorobenzene is, or is not, carcinogenic. There is enough evidence to suggest that MCB causes dose-related target organ toxicity, although the data are lacking for an acceptable chronic toxicity study. There is little, if any, usable human exposure data primarily because the exposure was not only to MCB but to other compounds of known toxicity.

A no-observed-adverse-effect level (NOAEL) for derivation of the water quality criterion can be derived from the information in the studies by Knapp, et al. (1971) and Irish (1963). These are 27.25 mg/kg/day for the dog (the next highest dose was 54.5 mg/kg and showed an effect), 12.5 mg/kg/rat from the Knapp study (the next highest dose was 50 mg/kg and showed an effect), and 14.5 mg/kg/rat from the Irish study (the next highest dose was 144 mg/kg and showed an effect). When toxic effects were observed at higher doses, the dog was judged to be somewhat more sensitive than rats. The duration of the study by Irish (1963) was six months which was twice as long as the Knapp study of two species (rat, dog). Since the Knapp and Irish studies appear to give similar results and since there are no chronic toxicity data on which to rely, the NOAEL level, 14.4 mg/kg for six months, from the longest term study (Irish, 1963) is used to calculate the acceptable daily intake (ADI).

Considering that there are relatively little human exposure data, that there are no long-term animal data, and that some theoretical questions, at least, can be raised on the possible effects of chlorobenzene on blood-forming tissue, an uncertainty factor of 1,000 is used. From this the ADI can be calculated as follows:

$$\text{ADI} = \frac{70 \text{ kg} \times 14.4 \text{ mg/kg}}{1{,}000} = 1.008 \text{ mg/day}$$

The average daily consumption of water was taken to be two liters and the consumption of fish to be 0.0065 kg daily. A bioconcentration factor of 10.3 was utilized. The following calculation results in a criterion based on the available toxicologic data:

$$\frac{1.008}{2 + (10.3 \times 0.0065)} = 488 \text{ µg/l}$$

Varshavskya (1968), the only report available, has reported the threshold concentration for odor and taste of MCB in reservoir water as being 20 µg/l. This value is about 4.5 percent of the possible standard calculated above. It is, however, approximately 17 times greater than the highest concentration of MCB measured in survey sites. Since water of disagreeable taste and odor is of significant influence on the quality of life and, thus, related to health, it would appear that the organoleptic level of 20 µg/l should be the recommended criterion.

Trichlorobenzene

Reliable toxicologic data on which to base a defensible water quality criteria do not exist for the trichlorobenzenes. The studies by Smith, et al. (1978), and Coate, et al. (1977) do not give sufficient detail or suffer from inherent problems in experimental design. Therefore, according to the guidelines for criteria derivation, a criterion cannot be recommended for any trichlorobenzene isomer. For future derivation of a human health criterion, sound data must be developed describing the effects of these compounds on humans and experimental animals. It should be emphasized that this is a criterion based on aesthetic rather than on health effects. Data on human health effects must be developed as a more substantial basis for deriving a criterion for the protection of human health.

Tetrachlorobenzene

The dose of 5 mg/kg/day 1,2,4,5-TeCB reported for beagles (Braun, 1978) was utilized as the NOAEL for criterion derivation. An acceptable daily intake (ADI) can be calculated from the NOAEL by using a safety factor of 1,000 based on a 70 kg/man:

$$\text{ADI} = \frac{70\ \text{kg} \times 5\ \text{mg/kg}}{1{,}000} = 0.35\ \text{mg/day}$$

For the purpose of establishing a water quality criterion, it is assumed that on the average, a person ingests 2 liters of water and 6.5 grams of fish. Since fish may bioconcentrate this compound, a bioconcentration factor (F) is used in the calculation.

The equation for calculating an acceptable amount of TeCB in water is:

$$\text{Criterion} = \frac{350\ \mu g/day}{2\ l + (1{,}125 \times 0.0065)} = 37.6\ \mu g/l \text{ or } 38\ \mu g/l$$

where:

2 l = 2 liters of drinking water consumed
0.0065 kg = amount of fish consumed daily
1,125 = bioconcentration factor
ADI = Acceptable Daily Intake (mg/kg for a 70 kg/person)

Thus, the recommended criterion for 1,2,4,5-TeCB in water is 38 μg/l. The criterion can alternatively be expressed as 48 μg/l if exposure is assumed to be from the consumption of fish and shellfish alone.

Pentachlorobenzene

A survey of the QCB literature revealed no acute, subchronic or chronic toxicity data with the exception of the study by Khera and Villeneuve (1975). These authors found an adverse effect on the fetal development of embryos exposed *in utero* to pentachlorobenzene administered to the dams at 50 mg/kg on days 6 to 15 of gestation. This dose constitutes a low-observed-adverse-effect-level (LOAEL). According to current guidelines, extrapolation from such data requires application of a safety factor of from 1 to 10. Since the observed effect was only suggestive of teratogenicity of QCB, a safety factor of 3 is applied. Because long-term toxicity data on humans is not available and the existing animal data is sparse, an additional safety factor of 1,000 is applied to the calculation of an acceptable daily intake (ADI) as follows:

$$ADI = \frac{70\ \text{kg} \times 50\ \text{mg/kg}}{(3)(1{,}000)} = 1.17\ \text{mg}$$

The average daily consumption of water was taken to be 2 liters and the consumption of fish to be 0.0065 kg daily. The bioconcentration factor for QCB is 2,125.

Therefore:

$$\text{Recommended Criterion} = \frac{1.17}{2 + (2{,}125 \times 0.0065)} = 74\ \mu g/l$$

The recommended water quality criterion for pentachlorobenzene is 74 µg/l. The criterion can alternatively be expressed as 85 µg/l if exposure is assumed to be from the consumption of fish and shellfish alone.

Hexachlorobenzene

Among the studies reviewed by this document, only two appear suitable for use in the risk assessment: the mouse study of Cabral, et al. (1978) and the hamster study of Cabral, et al. (1977). These two studies are described in detail in Appendix I.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities". HCB is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of HCB in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be unfeasible in some cases, and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of HCB corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5}, for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{06}, or 10^{-7} as shown in the following table:

Exposure Assumption (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 grams fish and shellfish. (2)	0.072 ng/l	0.72 ng/l	7.2 ng/l
Consumption of fish and shellfish only.	0.074 ng/l	0.74 ng/l	7.4 ng/l

(1) Calculated from the linearized multistage model described in the Human Health Methodology Appendices to the October 1980 Federal Register notice, which announced the availability of this document. Appropriate bioassay data used in the calculation of the model are presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly

proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Ninety-seven percent of the HCB exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 8,690-fold. The remaining 3 percent of HCB exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of HCB (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding HCB concentrations and (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding HCB concentrations. Because data indicating other sources of HCB exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

Summary of Recommended Criteria for Chlorinated Benzenes

Substance	Criterion	Basis for Criterion
Monochlorobenzene[1]	20 μg/l	organoleptic effects
Trichlorobenzene[2]	none	organoleptic effects
1,2,4,5-Tetrachlorobenzene	38 μg/l	toxicity study
Pentachlorobenzene	74 μg/l	toxicity study
Hexachlorobenzene[3]	7.2 ng/l	carcinogenicity

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[1] A toxicological evaluation of monochlorobenzene resulted in a level of of 488 μg/l; however, organoleptic effects have been reported at 20 μg/l.

[2] Insufficient data to derive criterion.

[3] The value 7.2 ng/l is at a risk level of 1 in 100,000.

APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Chlorinated Benzene*

Monochlorobenzene (MCB) is used industrially as a solvent, and as a synthetic intermediate primarily for production of phenol, DDT, and aniline. MCB has been detected in water contaminated by industrial or agricultural waste, and human exposure is mainly via water. There are no studies available concerning the mutagenic or carcinogenic potential of MCB, so that it is not possible to calculate a water quality criterion on the basis of an oncogenic effect.

There are three isomers of trichlorobenzene (TCB). 1,2,4-TCB is used as a carrier of dyes, as a flame retardant, and in the synthesis of herbicides. 1,2,3-TCB and 1,3,5-TCB are used as synthetic intermediates, while a mixture of the three isomers is used as a solvent or lubricant. TCBs are likely intermediates in mammalian metabolism of lindane, and TCBs metabolize to trichlorophenols (TCP), e.g., 1,3,5-TCB produces 2,4,6-TCP. TCB is present in drinking water, but there are no studies concerning the mutagenicity or carcinogenicity of these compounds and, hence, a criterion cannot be calculated on this basis.

Tetrachlorobenzene (TeCB) exists as three isomers. Two of these, 1,2,4,5-TeCB and 1,2,3,6-TeCB, are used in the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenol (2,4,5-TCP). TeCB is one of the metabolites of hexachlorobenzene and lindane. TeCB has not been identified in water in the United States. However, industrial effluent may contain TeCB which causes contamination of aquatic organisms. Soil microorganisms can metabolize lindane to TeCB, which may further contaminate water due to soil runoff. There are no carcinogenicity studies available for TeCBs so that a water quality criterion cannot be derived on this basis.

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*This summary has been prepared and approved by the Carcinogens Assessment Group of EPA.

Pentachlorobenzene (QCB) is used mainly as a precursor in the synthesis of the fungicide pentachloronitrobenzene, and as a flame retardant. Lindane metabolizes in humans to QCB. QCB has entered water from industrial discharge, or as a breakdown product of organochlorine compounds. There are no data available concerning the mutagenicity of QCB. There is a translated abstract of an article by Preussman (1975) which states that PCB is carcinogenic in mice, but not in rats and dogs. The abstract does not report the data and, since the article has been difficult to obtain, the study is not yet available to evaluate for a water quality criterion.

Hexachlorobenzene (HCB) is used as a fungicide and industrially for the synthesis of chlorinated hydrocarbons, as a plasticizer, and as a flame retardant. HCB has been detected in water near sites of industrial discharge and leaches from industrial waste dumps. HCB is very stable in the environment and bioaccumulates, so that it is present in many food sources, e.g., cereals, vegetables, fish, meat, and dairy products. It is stored in human adipose tissue and is present in human milk. There is only one mutagenicity study reported for HCB which is negative for the induction of dominant lethal mutations in rats.

Studies by Cabral, et al. (1977, 1978) indicated that oral administration of HCB induced hepatomas and liver hemangioendotheliomas in male and female Syrian Golden hamsters, and hepatomas in male and female Swiss mice. The data from the hamster study were reported in detail for evaluation, whereas the mouse study was only described in an abstract. In the hamster study, there was a statistically significant incidence of hepatomas in males fed 50, 100, and 200 ppm ($p = 7.5 \times 10^{-7}$, 2.45×10^{-15}, and 1.30×10^{-19}, respectively), and of liver hemangioendtheoliomas in males fed 100 and 200 ppm ($p = 4.5 \times 10^{-3}$ and 4.0×10^{-6}, respectively). There was a statistically significant incidence of hepatomas in females fed 50, 100, and 200 ppm ($p = 7.5 \times 10^{-7}$, 2.0×10^{-8} and 3.05×10^{-19}, respectively), and of liver hemangioendotheliomas in females fed 200 ppm ($p = 0.026$).

The water quality criterion for HCB is based on the induction of hepatomas in male Syrian Golden hamsters given daily oral doses of 50, 100, or 200 ppm (Cabral, et al. 1977). The concentration of HCB in drinking water calculated to limit human lifetime cancer risk from HCB to less than 10^{-5} is 7.2 ng/l.

SUMMARY OF PERTINENT DATA

The water quality criterion for HCB is based on the induction of hepatomas in male Syrian Golden hamsters given a daily oral dose of 4, 8, or 16 mg/kh for 80 weeks (Cabral, et al. 1977). The hepatoma incidences, in the treated and control groups are shown in the table below. The criterion was calculated from the following parameters:

Dose mg/kg/day)	Incidence (no. reporting/no. tested)
0	0/40
4	14/30
8	26/30
16	49/57

le = 560 days

Le = 560 days

L = 560 days

w = 0.100 kg

R = 8,960 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 1.688 $(\text{mg/kg/day})^{-1}$. The resulting water concentration of HCB calculated to keep the individual lifetime cancer risk below 10^{-5} is 7.2 ng/l.